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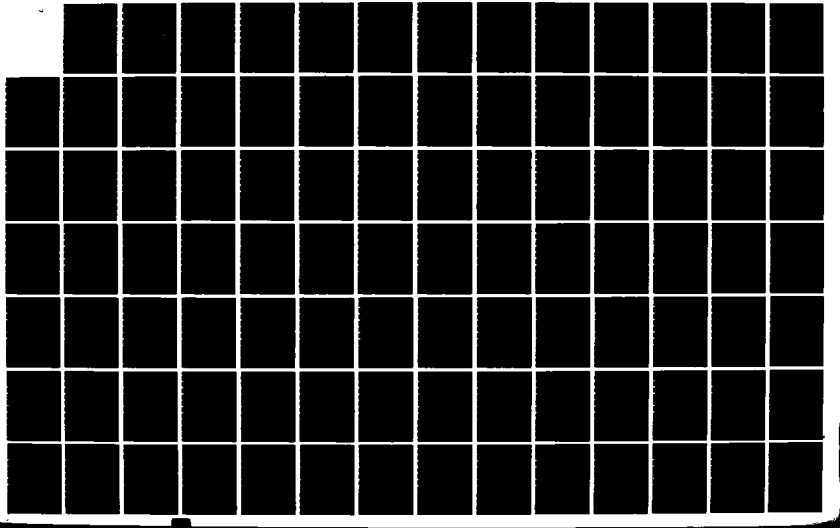

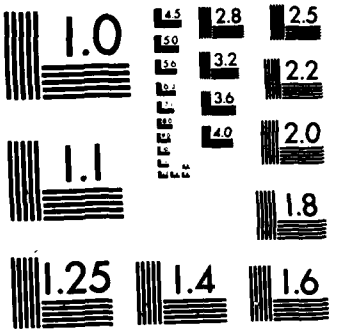

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A PROGRAM FOR CLINICAL CARE IN PHYSICAL TRAUMA

Final Report by Responsible Investigator:
Francis D. Moore, M.D.
Moseley Professor of Surgery, Emeritus,
Harvard Medical School;
Surgeon-in-Chief, Emeritus,
Peter Bent Brigham Hospital
Boston, Massachusetts

March 1, 1981

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U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract No. DADA 17-73-C-3022

Harvard Medical School
Department of Surgery at the Peter Bent Brigham Hospital
and The Brigham and Women's Hospital

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

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Francis D. Moore, M.D., Moseley Professor of Surgery, Emeritus
Harvard Medical School; Surgeon-in-Chief, Emeritus, Peter
Bent Brigham Hospital, Boston, Massachusetts.
Contract No. DADA 17-73-C-3022

SUMMARY - ABSTRACT

This final report ~~of contract work~~ covers studies ~~during~~ the past five years, tracing their proximate origin to results of the previous five years, at the Department of Surgery of the Harvard Medical School at the Peter Bent Brigham Hospital, Boston, MA. The final report, therefore, covers work carried out through the decade of the 1970s.

The work is in surgical metabolism, the biochemistry of convalescence from severe injury, the care of the injured, the care of the wounded, and covers both practical, clinical and theoretical-research aspects. For reasons of brevity and convenience of presentation, the final report is presented in paragraph form. Each paragraph covers one salient point or area of result; following this, the detailed bibliographic references are presented.

This laboratory is up to date with its publications, save for work done in the last few months. A bibliography of publications (Appendix B) and copies of unpublished texts (Appendix A) are presented herewith to provide additional background data.

The work covers four major areas. Most of the work has been carried out as clinical investigation (i.e. studies in man). A few ancillary studies in animals have been used to illuminate special problems.

The studies covered include the following: (1) Substrate utilization, substrate interaction and the endocrine effects observed in intravenous feeding after injury; (2) The use of isotopes of nitrogen and hydrogen in substrate research in man; (3) The pathophysiology of burns with particular respect to lung injury; computer

modelling in burns; acute hemorrhage in normal man as an acute trauma model; (4) Synthesis of knowledge in this field for undergraduate and postgraduate teaching of sugical care.

Outstanding findings of this research include: (1) Maximum protein synthetic capability on the intravenous administration of amino acids is only realized with adequate caloric support, such caloric support being required in extra large amounts in patients after severe injury; (2) Using isotopic heavy nitrogen it was shown that this difference in utilization is due to an increased synthetic rate when exogenous calories are supplied in support of amino acid infusion in man; (3) Burns not involving the airway produce an early low pressure pulmonary edema that interferes with pulmonary function, but its long term monitoring with indwelling pulmonary artery catheters is hazardous and can produce fatal endocarditis; (4) The previously healthy male subject faced with repeated hemorrhage makes a physiologic choice, choosing to restore volume to 90% normal at the expense both of total oxygen transport capacity and relative red cell mass.

I. SUMMARY OF PROBLEMS ADDRESSED, STUDIES UNDER THE CONTRACT, AND FINDINGS

A. Practical, Clinical or Tactical Problems Addressed and Summary of Findings

1. Caloric Support for Protein Synthesis and Intravenous Feeding

Findings:

The addition of calorie support from glucose, glycerol or fat improves the utilization of amino acids infused intravenously. The ideal mix depends upon the clinical state of the patient. Calorie:nitrogen ratios as high as 200-250 non-protein calorie/gram nitrogen are required after severe injury. In chronic starvation without stress, very low calorie:nitrogen ratios, in the range of 36-100 non-protein calories/gram nitrogen, are satisfactory.

References: II (2, 3, 8, 12, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24)

2. Peripheral versus Central Vein Infusion Sites for Intravenous Feeding in the Wounded, Starved, or Critically Ill

Findings:

The peripheral vein site is satisfactory for most intravenous feedings; the catheter must be placed in a large vein with non-occlusive attachment; calorie:nitrogen ratios of 36-100 are readily infused by this method. The available dose of nitrogen is satisfactory. If intravenous fat (500 ml) is added three times a week, an overall improvement in balance is achieved. When, following severe injury, or with sepsis, the calorie:nitrogen ratio mandate is in the range of 150 or higher, central vein

feeding must be used. The addition of fat in conservative amounts (500 ml three times per week) supports protein synthesis without unnecessary expense.

References: II (2, 14, 21, 22, 24)
V (5)

3. Substrate Interactions; Comparative Roles of Glycerol, Fat, and Glucose

Findings:

In starvation, endogenous fat oxidation without nitrogen support has little effect on nitrogen balance. Exogenous fat has the same "blank" effect. If nitrogen is provided (intravenous amino acids, protein hydrolysate or oral use of enteric nitrogen preparations), then the addition of fat improves the nitrogen economy. The relative effectiveness of glucose and fat suggests that ATP regeneration from glucose is more efficient for the support of peptide bond synthesis than is that resulting from fat or ketone oxidation. The data of these laboratories do not support any special role of ketones beyond their simple caloric support function. Glycerol is a carbohydrate-alcohol that yields the same caloric effect as glucose. It is present in all fat emulsions and is yielded by hydrolysis. We do not recommend its routine use for clinical support. Our laboratories have undertaken studies of glycerol with the object of elucidating the intermediary metabolism of 3-carbon compounds, rather than as a recommendation for clinical use.

References: II (2, 8, 12, 14, 16, 19, 22, 23, 24)

4. Effect of Trauma, Stress and Sepsis on Caloric Needs

Findings:

The calorie:nitrogen slope is left-shifted in simple starvation, favoring nitrogen economy at low calorie:nitrogen ratios (as mentioned above). In trauma and stress this curve is shifted sharply to the right indicating an increased mandate of caloric support. It is our interpretation that this increased caloric support requirement is due to competing needs in the organism, particularly those for the maintenance of elevated body temperatures, and increased work of respiration and circulation. There appears to be a limit to the ideal calorie:nitrogen ratio. Fragmentary data from our laboratories as well as from others suggest that one should use calorie:nitrogen ratios over 300 with caution, particularly where there is severe injury or illness, because of the possibility of liver damage.

References: II (5, 7, 17)
V (3, 4, 5, 7)

5. Possible Adverse Effect of Long In-Lying Central Catheters for Monitoring Cardiopulmonary Function

Findings:

Our suspicion of hazards was borne out by the finding of several patients with bacterial endocarditis. It is our conclusion that in the presence of severe wounds, compound injury or burns, the Swann-Ganz or indwelling type of cardiopulmonary catheter should never be left in more than one hour, and that the use of indwelling central vein catheters for feedings, though less hazardous, still impose a hazard. It is for this reason that peripheral vein feeding (mentioned above) is particularly favored.

References: IV (18)

6. The Effects of Branched Chain Amino Acid Solution Given Intravenously

Findings:

A solution composed exclusively of branched chain amino acids (leucine, isoleucine and valine) was made up by a pharmaceutical company in Scandinavia. This solution was approximately isotonic. Its purpose was not to advocate any such unbalanced solution for clinical use, but rather to study under laboratory conditions in the animal and in man the effects of such solutions.

The findings in animals showed no remarkable nitrogen sparing activity. In dogs an acute hyperuricemia was produced and a tendency to hypoglycemia. A few experiments were done in man. They had no adverse effects. Nitrogen sparing was not remarkable in any regard; there was a tendency towards hypoglycemia. There was no hyperuricemia. On the basis of these expermients, we did not deem it advisable to carry forward with additional extensive experimentation.

From this experience we learned that the current popular trend to very slight enrichment of ordinary amino acid solutions with small additional amounts of branched chain amino acids, had no apparent basis for widespread use. The molar concentration of branched chain amino acids is already high in standard amino acid solutions and in ordinary meat, as eaten.

References: II (25)

7. Ratio of Branched Chain Amino Acids to Total Amino Acids in Blood as a Measure of Catabolic/Anabolic Balance (BCAA/TAA Ratio)

Findings:

These observations were a byproduct of our work on substrate utilization. This ratio is a delicate index of the balance between supply and utilization of branched chain amino acids. Since these amino acids are present in all proteins in the body, it is evident that the ratio may have special significance in establishing the anabolic or catabolic state of an individual at a given point in time. If large amounts of glucose are given with nothing else, this ratio falls to very low levels, suggesting that these substrates are being utilized faster than they are supplied and that the body might be considered as "starving" for the substrates from which protein is synthesized. If large amounts of amino acids are given intravenously without any glucose, the ratio goes to a very high level, suggesting that the substrate is being supplied faster than the body can use it, because of the lack of sufficient support energy. If amino acids are given with glucose, the levels of anabolism and catabolism suggest a healthy synthetic balance, because the BCAA/TAA ratio is normal or nearly normal. It is of interest that intravenous fat emulsion and glycerol also normalize this ratio but far less efficiently than glucose.

References: II (24)
V (5)

8. Hemorrhage in Previously Healthy Men

Findings:

This work occupied several years (1970-74) and documented in detail the metabolic, biochemical, endocrine and hemodynamic changes with hemorrhage of moderate magnitude in normal man, and repeated hemorrhages (3 during the same week) as a more major stress. Major findings were those metabolic alkalosis resulting evidently from a volume-reduction stimulus, the production of aldosterone, with an increased aldosterone secretory rate; a rate of transcapillary refilling of the blood volume from the interstitial fluid that was predictable and was affected by the use of certain drugs, and by the fact that a normal healthy young male, threatened with repeated hemorrhage, is forced to make a physiologic adaptive choice: whether to restore volume fully at the expense of oxygen transport capacity, or whether to maintain the hematocrit but with inadequate volume. In all instances studied, volume restoration was virtually complete, lacking only 10% of complete refilling; oxygen carrying capacity is this maintained though short of total restoration as red cell resynthesis is far slower than plasma volume refilling. These data were then extended to clinical surgical observations on preoperative bleeding, the so-called hemodilution techniques, and the effect of such changes on body composition and pulmonary function.

References: II (8)
IV (8, 9, 10, 11, 14, 16)

9. Starvation in Previously Healthy Men

Findings:

These studies covered several years during the period 1971-1975. It was possible to "titrate" the urine nitrogen excretion down to an irreducible or "floor" minimum (approximately 1.8 gmM/M^2/day) by the administration of isocaloric amounts of glucose. The kinetics of this glucose-induced reduction in nitrogen wastage were of outstanding interest, including an anomalous rise in alanine concentration during glucose administration in starvation, suggesting that the "glucagon cutoff" that is associated with the administration of glucose results in decreased mobilization of alanine from muscle stores. While it is clearly inadvisable to treat starving patients with glucose alone, the molecular reaction between body protein kinetics on the one hand, and the oxidation of glucose on the other, command universal attention in the field of parenteral nutrition. It is also clear that a period on 1-8 days on glucose nutrition alone intravenously is not harmful in any way, and far to be preferred over intravenous fluid management with electrolytes in such compounds as lactate in low concentration.

References: II (2, 3, 8, 10)

B. Problems of Theory and Research Method Addressed and Summary of Findings

1. Tritium-Tagged Glucose as a Research Tool

Findings:

Glucose tagged with tritium in the 2-position is an effective method for measuring the body water available for glucose solution, the fraction of that body water within cells, and the glucose disappearance rate by oxidation. The latter is rendered more meaningful by the appearance of the oxidized tritium as THO in body water, which, by indirect means, provides a measurement of total body water. The limitation of the method has to do with recycling of lactate and the caloric uncertainties due to apparent disappearance rate based on tritium tag loss into lactate.

References: III (3, 4)

2. Heavy Nitrogen Tagged Glycine as a Method for Studying Protein Turnover; Intentional Curve Perturbation as a Model for Acute Illness

Findings:

The method of N^{15} glycine infusion as a means of studying whole body protein turnover has been established in these laboratories. The method is not original; very accurate measurements of intake and output of nitrogen are essential to interpretation. We have confirmed again the elevated total body protein turnover produced by acute injury and burns. Studies of the effects on this turnover of various caloric supplements were disappointing for reasons of time. Intentional perturbation of the curve by sudden doubling of the nitrogen intake or its sudden cessation were studied both as models for assessment of the mathematical treatment of

the curve itself, and as a means of reproducing in normal human volunteer subjects some of the perturbations that would occur in the care of acutely ill patients.

By priming the curve it was possible to shorten the period of equilibrium attainment. The method holds promise, but will probably not revolutionize any practical concepts in this field.

References: III (1, 2, 5, 6)
V (5)

3. The Study of Normal Volunteer Human Subjects as Models for an Understanding of Human Physiology and Pharmacology

Findings:

With elaborate precautions for informed consent and assurance of hazard reduction, normal human volunteers of the young male age group have been found remarkably important for all aspects of study and human nutrition, physiology, and pharmacology. It is impossible to interpret the findings in acute injury, wounds, trauma, combat casualties, fractures, and burns unless the findings in the normal young male are well understood. Many flagrant examples in the literature of wasted funds have been revealed, wherein studies were reported as showing changes due to trauma or injury, when, in point of fact, these changes would have been observed in perfectly normal people. The importance of this sort of control study cannot be over-emphasized so long as DOD funds are to be invested in clinical or surgical research.

References: I (11)
V (5)

4. Histologic and Biochemical Study of the Dog Vein as a Model for Peripheral Vein Tolerance

Findings:

By the employment of constant infusion of feeding solutions in the forelimb vein of an animal, it is possible by sequential biopsy and the use of controlled sides, to carry out observations that would be impossible in man. Histologically, the effects of extremely irritating hyperosmolar solutions are disappointing. There is an increased production of agglutination accelerator factors from the vein wall. Such might prove to be a promising avenue for further investigation. On the whole, the dog vein preparation was disappointing. Symptomatic production of painful peripheral veins in man is evidently accompanied by few histologic changes in corresponding solutions in the dog. Despite this limitation, it was shown that solutions up to 800 mOsm/L are tolerated in human peripheral arm veins so long as the vein is a large one and a non-occlusive attachment is employed.

References: (Unpub.)

5. A Theoretical Construct of the Endocrine Response to Severe Injury Has Resulted From These Studies

Findings:

It appears that the endocrine response to acute volume reduction underlies most of the endocrinology of stress, trauma, and post-traumatic catabolism. This adrenalmedullary catechol-amine response in turn stimulates the production of hydrocortisone, and glucagon, while inhibiting both the production and peripheral effect

of insulin. The "Post-traumatic pseudodiabetic state" results from this endocrine imbalance. The stimulation of aldosterone (see above under "Hemorrhage in Normal Man) also results from primary volume reduction but without the necessary intermediacy of the catechol-amines.

References: II (3,4,5,7,11,15)

6. Reference Models for Isotope Dilution Studies in Man

Findings:

A set of mathematical equations and body compositional reference models were constructed, worked to computer applicability, and published accordingly for: tritium (tracer for hydrogen), radio potassium, radio sodium, tagged erythrocytes and radioactive bromine. These constructs are helpful to workers in the field, especially those concerned with body compositional studies.

References: I (9)

7. Animal Models for Pulmonary Edema Studies

Findings:

Using special methods in the dog, and finding reflections of these artificial changes in certain clinical situations in man, it is clear that pulmonary edema (both alveolar and interstitial) can be associated with elevated left heart chamber pressures, in which case it is known as "high pressure edema", or may contrariwise, be associated with perfectly normal chamber pressures ("low pressure

edema"). This is an important differentiation in the surgical patient, since individuals presented with excess fluid loads particularly lacking in colloid oncotic pressure, may develop low pressure edema that gives every appearance of congestive heart failure, but will not respond to digitalis. Contrariwise, such low pressure edema will respond to diuretics and it is our impression, unproven, that in the diuresis that results, lung water finds a disproportionately high representation as a fraction of total body water. The early lung edema of the burned patient (see above) is a low pressure edema.

References: IV (1, 2, 3, 4, 5, 13, 14, 15, 16, 17)

8. Use of Instream Catheter for Patient Monitoring Findings:

This method has been widely used, both in this country and abroad; our studies merely served to standardize methods and results as well as call attention to hazards (see above under catheter induced endocarditis).

References: IV (6, 10, 12, 13, 15, 18)

9. Forearm Metabolism as a Model for Study of Muscle Changes

Findings:

The isolated forearm as a metabolic preparation has been standardized in this laboratory in collaboration with Dr. Thomas Aoki, of the group of Dr. George Cahill at the Joslin Laboratories. Our studies have demonstrated the flux of amino acids across the forearm muscle, the interpretation of these changes in the light of total body metabolism, the influence of carbohydrate on muscle utilization of amino acids, and the fact that some amino acids are carried in part in the erythrocyte and appropriate corrections must be made for amino acid flux across muscle beds.

References: II (10)

C. Inconclusive Findings or Problems Laid Aside as Unpromising

1. Purine Metabolism in Laboratory Animals

Findings:

These studies were initially undertaken to assess the importance of changes in purine metabolism and purine recycling after injury. If the supply of purines and pyrimidines ever become limiting for cellular replication and nucleic acid synthesis, particularly in the healing wound or fracture, such problems could become important. These studies were undertaken by Dr. O'Connor, but were not pursued as the initial results were

unpromising.

References: (Unpubl)

2. Lung Water in Burns and Pulmonary Edema and Hemodilution

Findings:

These findings, initially outlined by Dr. Morgan, showed that even in burns not involving the airway, there was some early increase in lung water in man. Much literature on this topic is confused by the fact that the pulmonary capillary is almost perfectly permeable to albumin. Increased permeability to oncotic molecules therefore has little to do with the accumulation of interstitial water in the lungs. Despite this limitation, it was possible to demonstrate that accumulations of long water contributed to the morbidity of burned patients and that the management of these accumulations by conservative therapy and use of diuretics was helpful. These findings were not original, had been shown by other investigators, and were not pursued further.

References: IV (1, 2, 4, 5, 13, 14, 15, 17)

3. Computer Program and Modelling Paradigm
Computer Retrieval Data Set for the Management of Human Burned Patients

Findings:

This work was undertaken by Dr. Morgan, Dr. O'Connor, and Dr. Fearon. The model is an attractive one. It should be possible to construct a closed loop feedback computer system to regulate the fluid therapy of burned patients. The problem was an ambitious one. Neither budget nor manpower available permitted its completion. It has been set aside, but all the data gathered are available for others should they wish to pursue the problem.

References: (Unpub.)

4. The Metabolic Effects of Glucagon

Findings:

We had reported that there was a tendency to an elevated glucagon after injury. Therefore, experiments were established to observe the effects of glucagon as a pharmalogical dose in man.

These experiments demonstrated that glucagon hastened nitrogen excretion in man, largely at the expense of small molecular weight nitrogen compounds already present in the extracellular fluid. This effect is acute and transient. For the most part, it does not appear to be a "catabolic hormone", but rather one that favors the excretion of nitrogen from small compounds, by dint of the synthesis of their carbon fractions into glucose.

To our suprise, however, it became evident that with prolonged administration of high dose glucagon there is some slight stimulation of additional catabolism in normal man. The effect is very small, even with glucagon levels far higher than one sees in injury.

There was no increase in the urinary excretion of 3-methylhistidine in these subjects, suggesting but not proving that the source of this catabolism was not to be found in peripheral skeletal muscle.

References: II (3, 4, 5, 6, 13, 24)

D. Military Relevance of this Research

The work done under this contract finds its military relevance in improvement in the management of injured patients, a better physiologic understanding of nutritional management and the metabolic utilization of intravenously supplied feedings. While this aspect of the treatment of the wounded may not predominate in most combat situations, it is an aspect of casualty management which may be of survival significance for some severely injured or wounded individuals and in burns.

The specific observations on bacterial endocarditis indicate the hazards of long indwelling intravenous catheters.

The observation on the usefulness of peripheral vein feeding would be of direct clinical application, even in forward hospitals.

Some of the closed loop computer work done in the laboratory might at some future time have application, but at the present time it appears still to be a research rather than a practical device.

Certain negative findings are of practical significance. The excessive use of intravenous fat emulsions is unnecessary; most of the caloric supply can come from glucose which is far less expensive. There seems to be no particular advantage in ordinary patients not suffering from liver or renal failure in using special branched chain amino acid solutions.

The current trend to slight enrichment of amino acid solutions by the addition of the branched chain amino acids cannot find any basis to support its greater expense and nuisance value in hospital

arrangements. These studies are based on individuals with normal renal and hepatic function. It is conceivable that with disordered function of kidneys and liver there may be distinct and clinical practical advantages to certain types of special amino acid solutions.

References: V (1, 2, 3, 4, 5, 6, 7, 8)

II. HISTORY OF THE LABORATORY, LOCATION, GOVERNANCE, AND PERSONNEL OVER THE PAST 15 YEARS

Army contract funding for this work has been an important component of the total laboratory enterprise over the course of many years. In account procedures and cost assessment of a laboratory enterprise of this type it is never possible to assess exactly the cost or contribution of any one fiscal component, nor is it possible to assign exact cost assessment to any one data analysis or retrieval component. Analyses, chemical procedures, biological assessments or laboratory examination of clinical undertakings may cross into several funding sources. Examples here relate to the assessment of critically injured persons, a study financed both by the Army, by the National Institutes of Health, by private fiscal charitable sources, by national foundations and by the home institutions, the Harvard Medical School and the Peter Bent Brigham Hospital.

In 1976 the laboratories of Dr. Moore were moved to the Good Samaritan Hospital; and in 1978 to the perimeter building of the new Affiliated Hospitals Center, later the Brigham and Women's Hospital.

In the summer of 1979 Dr. Douglas W. Wilmore came to take charge of the laboratories and to work collaboratively with Dr. Moore, learning of the methods of the laboratory, and taking an active part in the work in its final 12 months.

The laboratory staff under the capable leadership of Miss Margaret R. Ball continued to be active in the analytic and quantitative analysis work associated with these studies.

The Laboratory for Surgical Research in Building E-2 of the Harvard Medical School has been a significant component part of this work whenever the model of small animals was required.

III. PERSONNEL OF THE LABORATORY

Permanent Staff

Director:

Dr. Francis D. Moore (From opening of Laboratories until 1 July 1979)

Dr. Douglas W. Wilmore (1979-)

Associate Director of Laboratory:

Dr. Alfred P. Morgan

Dr. Murray F. Brennan

Dr. Nicholas E. O'Connor

Permanent Laboratory Analytic and Biochemical Section

Margaret R. Ball (Associate in Surgery)

Lourdes Holejko

Michael Colpoys

Anna Kaszowka

Mary Kowalczik

Arthur T. Finnegan

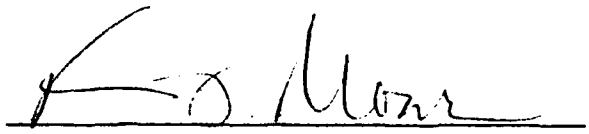
Physicians and Ph.D. Scientists who have worked in the Laboratories during the past decade include approximately 40 young men and women doing research assistantships and approximately 30 technicians who work here for 1-3 years each. Detailed list submitted on request.

Final Report by Responsible Investigator

Contract No. DADA 17-73-C-3022
U.S. Army Medical Reserach and Development Command
Fort Detrick, Frederick, Maryland 21701

Harvard Medical School
Department of Surgery at the Peter Bent Brigham Hospital
and The Brigham and Women's Hospital
Boston, Massachusetts

This final report is submitted by and has the approval of



(Responsible Investigator)
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Boston, Massachusetts

March 20, 1981

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A Program for Clinical Care in Physical Trauma

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Contract No. DADA 17-73-C-3022

Final Report
March 1, 1981

APPENDIX A

Previous Research Reports and Unpublished Prior Texts and Illustrations

Peripheral Venous Feeding Studies

Isotopic Nitrogen Studies

Protein Metabolism: Effect of Disease and Altered Intake on the Stable ^{15}N Curve

Annual Report 1977-1978

Progress Report 1975-1976

A Fatal Case of Endocarditis with Indwelling Line

The Development of Mathematical Models of Burn Fluid Pathophysiology

Effect of Calories on Nitrogen Balance (Illustration)

Nitrogen Metabolism on Various Substrates (Illustration)

The Effect of Hormone and Substrate Infusion on Glucose Dynamics in Man Using (2-^{3}H) Glucose as the Tracer

Research Horizons in Hospital Nutritional Support

A PROGRAM FOR CLINICAL CARE IN PHYSICAL TRAUMA

I. METABOLIC STUDIES

Brief Background and Progress Report

A. Peripheral Venous Feedings Studies

Patients who are chronically ill, starved, or chronically wasted display an avidity for protein precursor substrates and an ability to utilize these at far lower calorie/nitrogen ratios than is true either in the normal, or in the stressed individual.

This circumstance makes it possible to provide intravenous feeding through a peripheral vein in many instances.

Work carried out in this unit under this contract has explored this topic extensively because it is of major, everyday, practical, clinical importance to the Armed Services, both in peacetime hospital units and under combat conditions.

Experiments have been carried out in animals, and confirmatory observations made clinically.

In animals the experiments have consisted in using solutions of various osmolalities and chemical composition in dog veins, followed by histologic and biochemical study of the vein wall.

These have demonstrated that osmolalities as high as 800 milliosmoles/liter are well tolerated in peripheral veins, so long as blood flow can continue in the vein. To our surprise and disappointment, we have not been able to demonstrate that the addition of intravenous fat constitutes a so-called "mollifying factor" in the intimal injury. Allegations based on soft data have been current for at least 10 years, that adding intravenous fat makes a given osmolality better tolerated in a vein. We cannot confirm this in animal models.

It is quite true that since intravenous fat emulsions are isotonic, adding them to peripheral venous mixtures allows one greatly to increase the calorie-nitrogen ratio without significant increase in osmolality.

On the clinical side, observations have been made of normal volunteer subjects with careful studies of nitrogen metabolism, and on a variety of clinical patients in whom peripheral intravenous feeding was indicated. All of these demonstrate the same general phenomena, namely:

1. With osmolalities of 750-900 milliosmoles/liter, the peripheral vein intravenous is well tolerated if the catheter does not cross a joint line and if it is changed at the first sign of irritation. In many cases, one is pleasantly surprised to find that a peripheral vein will hold intact for 7 to 12 days of this type of feeding.

2. The vein selected should be large and the mode of occlusion of the intravenous catheter should be such that the vein flow of blood is uninterrupted.

3. Using these methods, calorie/nitrogen ratios of 36-96 are easily obtained. With such support using purified amino acid solutions, and either carbohydrate or fat or a mixture of the two as calorie support, satisfactory nitrogen balance and good evidence of whole body synthesis are easily obtained.

4. Using isotopic studies (see below) it can be shown that good synthetic activity accompanies such infusions.

In summary, these data show the practical availability of peripheral vein feeding in many clinical situations. Such feedings avoid the hazards of central vein catheters including pneumothorax, air embolism, hypertonic overloading, and sepsis. Such peripheral vein feedings are not adapted to all clinical situations, but when available, represent a marked advance.

B. Isotopic Nitrogen Studies

Our studies with N^{15} enriched glycine have now entered their third year with remarkably interesting and seemingly important findings.

An initial report has been published recently in "Lancet" (enclosed).

The method is that of the constant infusion of the isotopic amino acid, together with the study of the isotopic enrichment of the urea nitrogen in the urine.

We have compared substrates with a view towards understanding the caloric support of protein synthesis and the energetics of peptide bond formation in the whole body.

All our studies have been carried out in man. This is a nonradioactive isotope and involves no special hazards.

The data clearly show that peptide bond synthesis in man requires caloric support. Amino acids alone are inefficiently utilized. This caloric support can arise from either glucose or fat. Calorie-for-calorie, glucose is more efficient than fat (Figure 1).

When feedings are given with low glucose alone, protein turnover is increased. This suggests that when the body is given an inadequate amount of glucose to satisfy its needs for that special molecular configuration, as well as being associated with a lower value for serum insulin, endogenous production of gluconeogenetic precursors is hastened, and this is reflected isotopically by an increased turnover rate.

These data are further being readied for publication, and a manuscript will shortly be prepared.

The practical importance here lies in a simple clinical rule. Namely, that where there is a limitation on the total amount that may be given intravenously, it is better to apply a constraint to the total amount of amino acids infused, covering them with adequate caloric supply, rather than to accomplish the financial and molecular wastage involved with giving pure amino acids, but with inadequate caloric cover.

As indicated above in this report, it is often possible to supply this need in peripheral veins, especially if the patient is unstressed.

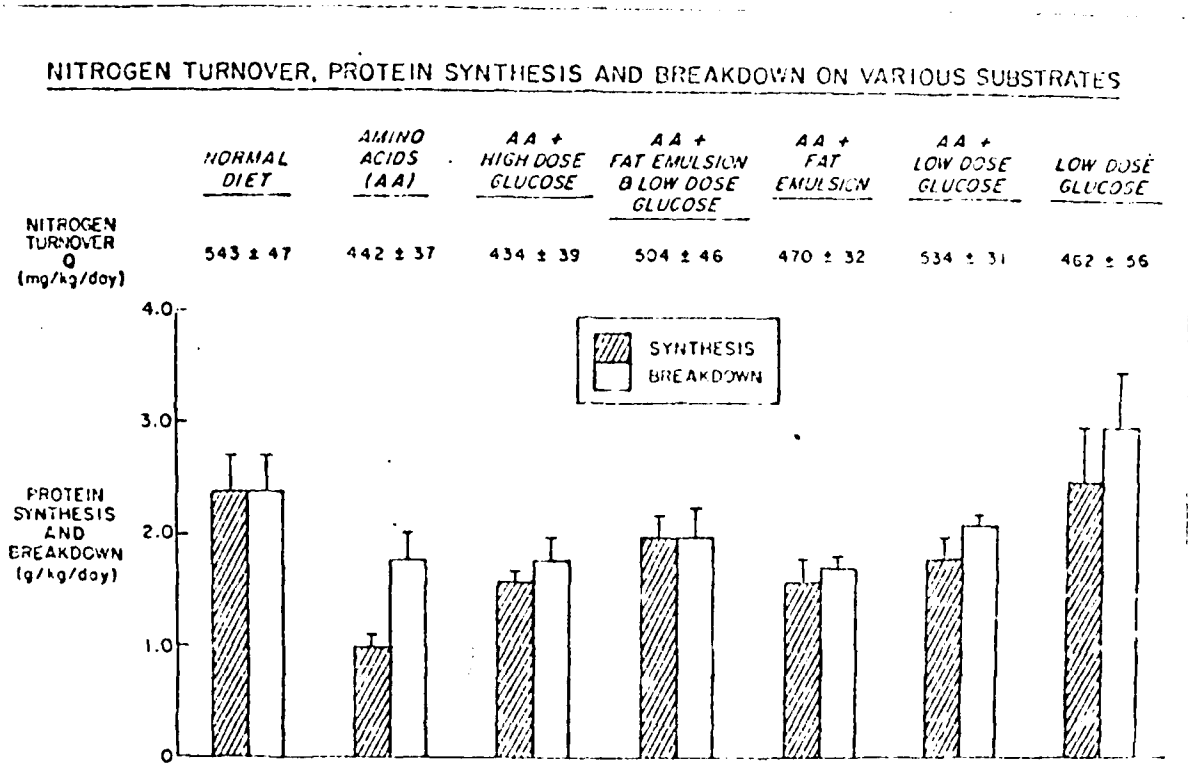

Figure 1: Above are shown whole body protein turnover data (Q), synthesis, and breakdown, for a variety of intravenous substrate mixtures studied in normal (fasting) human volunteer subjects. The three columns to the left (oral diet, amino acids alone, and amino acids with high dose glucose) demonstrate a reduction in Q when shifting to intravenous diet, and a clear increase in synthesis rate with added glucose. The four columns to the right (substrate mixtures as shown above each column) confirm the effect of added energy sources on synthesis rates; the column to the extreme right (low dose glucose alone) suggests an increased protein turnover rate on subcaloric carbohydrate without nitrogen.

PROTEIN METABOLISM: EFFECT OF DISEASE AND ALTERED INTAKE ON THE STABLE ^{15}N CURVE

Virginia M. Herrmann, MD, David Clarke, MS, FRCS, Douglas W. Wilmore, MD, FACS, Francis D. Moore, MD, FACS

Nitrogen economy is adversely affected in patients with various diseases. This may be due to a decrease in protein synthesis, increased catabolism, or both. Continuous administration of ^{15}N-enriched glycine (^{15}N gly) is used to estimate whole body protein turnover (Q), synthesis (S), and catabolism (C).[1,2] Alteration of the steady state by acutely changing protein and calorie intake allows examination of the effects of acute nutritional and metabolic changes on Q, S, and C in normals.

MATERIALS AND METHODS

All subjects were maintained on intravenous (IV) or oral diets to provide at least 30 Kcal/Kg-day and 1 gram protein/Kg-day. Six male control subjects (age range 18-30 yr.) were maintained on oral diets of 4 equally spaced meals daily. ^{15}N gly was administered continuously by IV infusion or oral dose given every 3 hours at 0.5 mg ^{15}N/Kg-day and steady state achieved as evidenced by an equilibrated enrichment plateau in urea ^{15}N excretion. After steady state was reached in volunteers at 72 hours, protein intake was doubled, or calories and protein withdrawn entirely. The investigation continued for 48 hours, and Q, S, and C reassessed at the end of that time. The new values in the metabolic unsteady state but with a new isotope equilibrium are referred to as the "apparent" Q at the new level.

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RESULTS

With adequate provision of calorie and nitrogen intake, Q was elevated in all patients studied, compared with fed normals (Table I). Doubling protein intake in normals acutely increased the apparent Q by 20.2%, 24 to 48 hours after the change in intake, while sudden cessation of protein and calorie intake produced a 40% decrease in apparent Q. With protein doubling minimal changes were noted in S, and a moderate decrease in C observed (18%). Cessation of intake caused a marked decrease in S (56.9%), with no significant change in C.

CONCLUSIONS

Acute perturbations of the steady state model can be assessed in patients as well as in normal man. Acute febrile illness, severe stress, and burns all produce a large increase in Q, S, and C; while increasing protein intake has some effect on Q and C, withdrawing protein intake lowers Q but has no effect on C. Q and C are greatly altered by acute disease processes. The metabolic response to these diseases heightens Q and C and contributes to the negative nitrogen balance associated with these illnesses.

TABLE I Protein Turnover, Synthesis and Catabolism in Patients

Patient	Age yrs.	Weight Kg	Diagnosis	Q mgN/Kg-day	Q gmN/day	S gmN/day	C gmN/day
Normal	25	70.0		506	34.2	23.9	22.2
G.P.	52	75.8	54% TBS* burn 17 PBD+	872	66.1	45.9	34.6
G.P.		71.0	30 PBD	748	53.1	32.9	22.6
A.B.	40	78.8	70% TBS burn 5 PBD	660	52.0	32.8	51.9
A.B.		64.0	38 PBD	979	62.7	50.2	34.6
D.P.	26	64.0	Abdominal sepsis	862	55.2	30.1	26.2
D.P.		51.5	Sepsis, GI bleed, post-operative	822	42.3	27.5	13.0
S.C.	28	66.5	Testicular Cancer Stage III, pre-chemotherapy	677	45.0	27.7	24.5
S.C.		66.5	Testicular Cancer post-chemotherapy	659	43.8	22.8	22.2

* TBS - Total Body Surface
+ PBD - Post Burn Day

Table II Effect of Acutely Altered Protein and Calorie Intake on Apparent Protein Turnover, Synthesis and Catabolism

	Dietary Intake		
	30 Kcal/Kg-day 1 Gm protein/Kg-day	30 Kcal/Kg-day 2 Gm protein/Kg-day	0 Kcal 0 protein
N	N = 8	N = 8	N = 4
Q mgN/Kg-day	505.7 ± 70	607.6 ± 91	303.6 ± 24
Q GmN/day	34.2 ± 8.5	41.0 ± 6.9	21.9 ± 4.5
S GmN/day	23.9 ± 6.5	25.2 ± 6.3	10.3 ± 4.9
C GmN/day	22.2 ± 6.2	18.2 ± 7.6	21.9 ± 4.5

ANNUAL REPORT - February 1, 1977 - January 31, 1978

A PROGRAM FOR CLINICAL CARE IN PHYSICAL TRAUMA

I METABOLIC STUDIES

Total Body Protein Turnover As Measured By N^{15} Enriched Glycine

During the past two years this method has been established in our laboratories and our first set of normal volunteer control experiments have been completed. These data are about to be published and were recently presented at the Society for Surgical Research at Helsinki, Finland by Dr. Sim of our laboratories.

These normal control experiments turned out to be unexpectedly interesting. We had five subjects who served as their own control on three separate occasions.

On the first occasion a normal, oral diet was taken with zero balance. On the second occasion the run included the provision of nutriments solely as intravenous amino acids without any other substrate or oral nourishment. On the third occasion the same infusion was given but with added glucose in the amount of 450 gms. per day.

Each one of the "runs" were for 7 days, yielding a very stable period for metabolic study. The N^{15} glycine technique was used by constant infusion over a 60-hour period at the close of each run.

The normal volunteer subjects, fasting, save for the measured intake indicated above, showed on normal diet a turnover of 3.4 gms. of protein/kg/day. Synthesis and catabolism were well balanced. On the intravenous regimens the turnover rate was markedly reduced to 2.6 gms. of protein/kg/day. This was associated with a reduction in synthesis and a normal level of catabolism as one would predict with a negative balance. With the added glucose there was a marked increase in synthesis which then balanced catabolism. This was a conclusive demonstration that when carbohydrate energy is added to amino acids there is an increased rate of protein synthesis than with amino acids alone.

Of unusual interest in this experiment was the demonstration that with intravenous intake the total body protein turnover or "Q" is reduced, as mentioned above. This reduction is interpreted as being due to a shutoff of pancreatic and gastrointestinal digestive enzyme synthesis. Without oral intake, the local secretory stimuli to the production of these enzymes are markedly reduced. The total weight of protein synthesized daily by these digestive glands and the pancreas may approximate 15-20 gms. This finding has not previously been reported and requires further work for additional interpretation.

When a nitrogen 15 enriched amino acid is infused and the degree of enrichment of urea in the urine measured, as with the N^{15} glycine method, one must be strict in the interpretation of what is being measured. Local recycling of amino acids in and out of protein without deamination will not be measured by the method. There is no low molecular weight pool of nitrogen compounds that can compete with the huge dilution volume of total body protein synthesis to account for the turnover rates. The turnover rate or "Q", is therefore the independent variable measured by this technique and is the important single number coming out of the mathematical treatment of the urea enrichment. This mathematical reduction of the data is extremely simple, its simplicity depending upon the 60-hour infusion and the attainment of a plateau. The patient's own body is therefore, the "integrator" in the differential equation for isotope incorporation into synthesis. This is the beauty of this method as opposed to single pulse injections.

A weakness of the method, however, is that the differential measurement of synthesis and catabolism depends upon numerical input from the measured nitrogen intake and output. The deduction of synthesis and catabolism from N^{15} glycine enrichment curves is therefore, not independent of the observed balance. This is important to emphasize, both in our work and in evaluating other work from the literature.

Effect Of Catabolic Hormones On Glucose Pools And Turnover

During the past two years, a series of experiments was carried out in which tritiated glucose was used as a tracer for measuring minimum glucose mass, glucose replacement rate and glucose space in man. A single injection of (2-^{3}H) glucose was used as the tracer. This method entails measuring a steady state distribution of the tracer, and then the amount of tritiated water that accumulates as the glucose is oxidized. This allows for an estimation of the rate of glucose oxidation, and the pool sizes.

Two sets of experiments were carried out with normal volunteer subjects. The first group of subjects was given infusions of glucagon, norepinephrine and then glucagon and norepinephrine combined, and the second group was given infusions of hydrocortisone and insulin. The effect of these hormone infusions then on minimum glucose mass, glucose replacement rate and glucose space were determined.

The results showed that when subjects were rendered hyperglycemic by glucagon, norepinephrine, and hydrocortisone infusion, minimum glucose mass and glucose turnover increased; the glucose space was unaffected. During insulin infusion glucose concentration fell significantly, minimum glucose mass fell to a lower degree, and the glucose replacement rate was increased sharply. There was an increase in the glucose space after insulin infusion suggesting that part of the fall in glucose concentration was due to the redistribution of the glucose in a larger space.

The interplay between hormones which raise or lower the serum concentration of glucose has long been recognized as a crucial factor in the control of glucose homeostasis. In these studies there was an elevation of the serum glucose concentration in response to infusions of glucagon with and without additional norepinephrine. There were also elevations of the serum glucose concentration with infusions of hydrocortisone. The addition of norepinephrine to glucagon infusion produced a more pronounced hyperglycemia. Glucagon alone and with norepinephrine also increased the glucose replacement rate. With glucagon, the hyperglycemia and increase in glucose replacement was a manifestation of a dynamic steady state establishing itself under the influence of this hormone.

Insulin alone on the other hand produced a hypoglycemia but with a sharp increase in glucose replacement rate. It is well known that a prime action of insulin is to enhance the transport of glucose across cell membranes, and part of the decrease in serum glucose concentration is to some degree caused by the redistribution of glucose throughout a larger space, and not necessarily wholly as a result of increased glucose utilization.

These studies demonstrate that changes in serum glucose concentration after hormone infusion are the result of a complex combination of alterations in glucose space and replacement rate. They help to explain the hyperglycemia seen following trauma and burns.

Amino Acid Infusions

The work in this laboratory on the utilization and metabolism of intravenous amino acids as the sole nutritional substrate in fasting normal human subjects has been completed and published. In the normal human subject, many variables can be controlled; the achievement of an ideal body fuel economy is quite simple; if a favorable utilization of injected foodstuffs cannot be achieved in this setting, it is unlikely, and remains to be proven that utilization will be satisfactory under the challenges of acute surgical trauma. In this experimental model, employing four normal human volunteer subjects, nutrition was provided by the intravenous infusion of isotonic amino acids (freamine #2) at a 3.4% concentration. No other source of calories or nutrients was provided. In this setting utilization was poor; the subjects were in negative nitrogen balance throughout the infusion period. The nitrogen excretion was significantly greater than the total of infused nitrogen. The changes in protein fat and carbohydrate intermediates, as well as the alteration in hormone concentrations suggest the following endocrine governance of fuel economy in this setting: a sharp rise in glucagon with maintenance of insulin concentration; rapid gluconeogenesis at the expense of both injected and endogenous amino acids; a progressive ketosis without any associated improvement in protein economy; fat oxidization to meet caloric need.

The changes in plasma amino acid concentrations are of outstanding interest. They demonstrate changes appropriate to the infusion gradient with the exception of three amino acids whose concentrations did not respond to high infusate levels (serine, lysine, alanine); likewise by the fact that methionine rose remarkably though present in low concentrations in the infusion. These data taken with other information reported in the literature, strongly suggest that the utilization of infused amino acids for protein synthesis is favored by the provision of an additional caloric source such as glucose.

Substrate Interactions

The studies of the comparative effects of carbohydrate and fat on amino acid utilization in fasting man have also been concluded and published. Data are presented on the metabolic and endocrine effects of intravenous infusions in normal fasting man observed under highly controlled conditions over a period of six to eight days duration. There are comparative data on a variety of intravenous feeding programs. The data on total starvation are based on studies from the literature, some of which were carried out in this laboratory. The data on low dose glucose, high dose glucose, glycerol, fat emulsion, and amino acids, each given separately, demonstrate changes seen with simple infusion of a single substrate in fasting. These data are now compared with the utilization of amino acid infusions when accompanied by low dose glucose, high dose glucose, glycerol, and fat emulsion. In all, nine experimental intravenous feeding programs are presented, based on data from 35 subjects observed over a total of 370 subject-days. The findings show a strong interaction between glucose or lipid and protein metabolism. In fasting, glucose had protein sparing effect, most evident when given at high dose. Glycerol, in an amount equal to that contained in 2000 ml of ten percent fat emulsion, had a mild protein sparing effect. Fat emulsion was no more effective. When amino acids were given alone, normal fasting human subjects were always in negative nitrogen balance with the daily nitrogen loss half that seen in starvation alone. Although amino acids given alone have a protein sparing effect, this is accomplished only at the expense of a high nitrogen excretion including an amount equivalent to the entire infusion plus an additional loss from the body's native proteins.

The provision of energy yielding non-protein substrates with the amino acids markedly improved nitrogen economy in the following order: glycerol, low dose glucose, fat emulsion and high dose glucose. When caloric provision with glucose approached the isocaloric level for normal diet, the utilization of amino acids was maximized. When given with amino acids, fat emulsion was more effective than the available glycerol alone.

The accompanying endocrine and biochemical changes suggest that the milieu for ideal utilization of infused amino acids is

variable: ketones at low range (carbohydrate) or moderately elevated (fat emulsion); insulin elevated (carbohydrate)or unchanged (fat emulsion). The utilization of the infused amino acids was markedly improved in both endocrine settings, suggesting that it is the provision of energy as substrate as well as the endocrine setting that determines amino acid utilization. There were other changes in plasma intermediates, particularly fatty acids, glucose and urea, all consistent with the concept that when amino acids are given without other substrates, the amino acids must be maximally utilized for gluconeogenesis. When other substrates are provided (particularly glucose at high dose) then this mandate no long exists and protein synthesis from the amino acids is favored.

Several of the plasma amino acid concentrations responded to glucose when added to amino acid infusion. Amino acids alone produced increases in concentration of all the amino acids found in the infusion with the exception of alanine, arginine, and threonine. Many of these increases were abated by the addition of glucose to the amino acid infusion, suggesting an increased utilization rate. Glycerol and fat emulsion, while modulating increases in the plasma amino acid concentration, did so to a lesser extent than did glucose. This lowering of amino acid concentration was unaccompanied by an increase in urinary excretion. The assumption is therefore made that the provision of the added glucose favors the incorporation of amino acid into protein. There is no evidence from these data to suggest that a rising concentration of ketones in the blood favors amino acid utilization or protein synthesis.

II PULMONARY STUDIES

Lung Water Changes After Thermal Burns

This study of sequential measurements of lung thermal volume was used to examine the natural history of pulmonary water changes with burn injury and its treatment. The study comprises results from nine patients with major thermal burns (20-80% body surface area). As soon as possible after initiation of acute-phase therapy LTV measurement was begun and repeated at least twice daily. Instead of the ordinary single lumen peripheral arterial catheter, a double lumen 5 French catheter placed in the radial artery by direct cutdown was used. The catheter was advanced until a phasic conductivity flow signal was obtained. The second lumen carried leads to a thermistor bead and platinum ring conductivity electrodes at the tip of the catheter. The lung thermal volume (LTV) was measured by the double indicator-dilution technique. The intravascular indicator was hypertonic saline solution which causes a change in blood conductivity measured by the conductivity electrodes. The extravascular indicator was a temperature pulse of cold water measured by the thermistor bead.

Most of the measurements of LTV in these patients yielded values that lay between normal and a range of clinical pulmonary edema. Frequently the lung thermal volume reached a maximum value within the first 24 hours and by 36 hours had declined to a minimum value at the same time the peripheral burn edema was at a maximum. Pulmonary capillary wedge pressures during acute phase therapy never exceeded 10 mm Hg in any patient. Therefore the increase in LTV represented a low pressure pulmonary edema. The initial high value of LTV is presumed to be the result of alveolo-capillary damage from inhaled or burn generated toxins. There was a secondary increase in LTV associated with dilutional hypoproteinemia during edema mobilization.

The possibility that pulmonary damage is caused by burn toxin is speculative but would help explain the very early increases in LTV that were observed. With or without a toxic component it appears that a moderate increase in pulmonary extravascular water is common in burn patients and universal in the group of patients studied here. It appears early in the course of injury, and is not high pressure pulmonary edema but is associated with dilutional hypoproteinemia. It appears early and subsides early to a minimum value at the time peripheral burn edema is maximum. Secondary increase may be associated with burn edema mobilization.

Pulmonary Function Studies Following Thermal Injury

Carbon monoxide poisoning and metabolic acidosis often constitute the major problems in early treatment of fire victims with smoke inhalation. Recently, there has been interest in defining prognostic factors in patients with carbon monoxide poisoning. Studies from other laboratories have suggested that carbon monoxide poisoning associated with an arterial blood pH below 7.4 led to early mortality or to serious neurologic sequellae if the patient survived. In this study of the pulmonary function changes seen with burns and smoke inhalation, three patients with severe acidemia and high carboxyhemoglobin levels were singled out for detailed review. All three patients were admitted with carbon monoxide saturation levels greater than 40%, and pH values below a level of 7.3. The patients were managed conservatively with prompt endotracheal intubation, ventilation and the administration of a hundred percent oxygen. All three patients survived without neurologic deficit.

Obstructive lung disease was the major problem in the convalescent care of the three patients. Pulmonary function tests performed during their initial hospitalization and up to six months after the time of injury revealed a severe obstructive ventilatory defect in these patients. This defect was minimally responsive to the administration of bronchodilators. This severe obstructive ventilatory defect is highlighted by marked decreases in forced vital capacity, forced expired volume, and reduction in maximal mid-expiratory flow rate. These findings contrast with those of other laboratories which have shown normalization of pulmonary function despite severe inhalation injury.

Patients with the combination of high levels of carboxyhemoglobin and low blood pH are effectively treated with intubation and ventilation with 100% oxygen. This therapy effectively prevents neurologic deficits, but does not obviate long term respiratory problems.

UNITED STATES ARMY - RESEARCH AND DEVELOPMENT COMMAND
Department of Surgery of the Harvard Medical School
at the Peter Bent Brigham Hospital
Dr. Francis D. Moore

Army Grant 1-20-77

PROGRESS REPORT - 1975-1976

The Metabolic Basis of Intravenous Feeding in Traumatized Patients

I SUBSTRATE INTERACTION - GLUCOSE, AMINO ACIDS, GLYCEROL, AND FAT

The work described in this section of the Report was done under the direction of Dr. Francis D. Moore in the Surgical Laboratories at the Peter Bent Brigham Hospital up to June 30, 1976. After that time the work was moved to Dr. Moore's new laboratories in the Good Samaritan Division of the Peter Bent Brigham Hospital. These laboratories have been established by the Board of Trustees of the Peter Bent Brigham Hospital specifically for this work. The quarters are ample and spacious. Our equipment has been moved without event. The laboratory move about which we had been apprehensive, had very little impact on the continuity of the work, thanks to the devoted efforts of the staff.

Doctor Moore was assisted in this work by his postgraduate research assistants; Dr. Peter Wright, Dr. Jesus Culebras, Dr. Bruce Wolfe and Dr. Andrew Sim. The analytic work was done under the immediate direction of Miss Margaret R. Ball with the assistance of Mrs. Lourdes Holejko, Mrs. Anna Kaczowka and Mrs. Katherine Cohen.

Man is the subject of these investigations. It should be emphasized that this laboratory over the years has concentrated on human studies; they are difficult and expensive to accomplish in many instances. However, the species differences in certain aspects of intermediary metabolism are notable. The work is established on The Clinical Center of the Peter Bent Brigham Hospital with the collaboration of the entire supporting staff of that Center. The subjects are admitted for satisfactorily long periods of time so that the biochemical data reach equilibrium. Changes are clear-cut and statistical significance levels are high.

1. Maximum Glucose Intake In Fasting Man

In prior experiments reported several years ago (O'Connell), we found that in normal fasting man the basal nitrogen excretion could be lowered to a minimum or floor level by glucose infusions at the approximate intake of 750 grams per day. The nitrogen sparing effect of carbohydrate was spectacular but there seemed to be a maximum achievable sparing effect at that level of intake. In the current experiments it was our object to determine if nitrogen excretion could be reduced to an even lower level by increasing glucose intake to excessively high values. As will be noted, the experiments had to be terminated because of symptomatology on the part of the subjects, a most interested finding in itself. Specifically, our object with the glucose infusions was to increase the intake to approximately 1000 grams of glucose a day. In two successive subjects, the observations had to be stopped because of unusual signs of illness and discomfort on the part of the recipient including right upper quadrant pain and a rise in liver enzymes. There was little overt sign of serious disorder upon physical examination but the subjects felt very uncomfortable and complained of headache. Blood chemical changes showed some elevation of glucose to a greater extent than was seen at the lower levels of intake. Hormone and amino acid results have not yet been returned; the experiments were discontinued.

These experiments teach an important lesson: that carbohydrate (as well as fat) given in excess of caloric requirements can produce unfavorable reactions that appear to be focalized in the liver. It will be recalled that about 1960, in experiments conducted under Army sponsorship and in part at the Walter Reed Army Institute of Research, it was demonstrated

that when Lipomul (a coconut oil fat emulsion then available and widely used) was infused intravenously in amounts grossly in excess of caloric requirements, there was severe subjective symptoms including fever and in some instances evidence of severe liver damage.

This demonstration of an analogous response with excessive glucose intravenous infusions, while only a small part of our work this past year, will be reported in the literature separately, because it serves as a warning, in the present period of enthusiasm for mixed high caloric intravenous feedings, that one must beware of providing caloric intakes grossly in excess of physiologic requirements, even though the components are entirely nonlipid in character.

2. Amino Acids As The Sole Substrate For Intravenous Provision In Normal Fasting Man

These experiments have been completed and mark the major achievement of the Spring of 1976. The analyses of amino acid levels have all been completed and returned. A manuscript has been accepted for publication in the Annals of Surgery and will appear within the next month or two. It appears to us that this is the most important contribution from our laboratory since the glucose and nitrogen sparing Paper referred to above.

The findings are of remarkable interest because they demonstrate for the first time, clearly and in man, that amino acids given alone in a quantity of approximating 90 grams per day (nitrogen intakes about 6 gms/M^2/d) does not result in a favorable protein economy. In normal fasting human subjects it instead produces a negative nitrogen balance. These are the most favorable possible circumstances for improving nitrogen economy and it is a remarkable finding that amino acids alone are unable to support the body cell mass. These experiments were carried out in four subjects hospitalized and cared for using the highly specialized protocol referred to in last years application. The periods of study approximate eight days in length and were long enough to permit full equilibration and provide entirely adequate interpretive basis.

Despite a progressive ketosis there was no improvement in nitrogen metabolism over the period of time observed. Insulin levels did not drop to starvation concentrations and glucagon rose briskly. There was evidence of conversion of essentially all of the infused material into glucose or other energy substrates, with the excretion of all the nitrogen as urea. In addition, since the patients were in a negative nitrogen balance approximating 3-4 gms/M^2/d it was clear that there was a continuing draft on the patient's endogenous protein stores to make up some biological deficit perceived by the body either in calories or specific carbon chain configurations. The amino acid preparation used was FreAmine II.

Plasma amino acid analyses have been completed and are included in the Report. Most of the amino acid concentrations behaved according to the infusion gradient. Only phenylalanine and methionine showed exceptions to this rule since they both rose briskly despite the fact that they were not present at high concentrations in the infusion.

In our published Report we make it clear that one cannot extrapolate from the normal human fasting volunteer to the many stressful details of the acutely traumatized patient. Nonetheless, we feel that the fasting normal human volunteer represents an optimal favorable situation for utilization of intravenous nourishments. If in such a setting one cannot achieve a favorable nitrogen economy it appears highly unlikely that the acutely or chronically traumatized or septic individual will have a favorable response. Unstressed starvation alone may improve nitrogen economy over the normal resting fast but this would not be the case with acute trauma or sepsis.

In conjunction with this work we have carried out some amino acid infusions in chronically starved surgical patients as will be mentioned below.

3. The Addition of Carbohydrate At Two Dose Levels To The Amino Acid Infusion

These studies have likewise been completed and are being prepared for publication.

They will be presented at the Spring meeting of the American Surgical Association. They involve the administration of glucose at low dose (approximately 150 grams per day) and at a high dose (approximately 750 grams per day) along with the same amino acid infusions given in precisely the same amount and composition as those mentioned above.

The effects of carbohydrate infusion on amino acid utilization and on body economy, are spectacular. At the low dose of glucose there was a marked improvement in nitrogen economy and at the higher dose a positive balance is readily achieved withthe amino acid infusions which, alone, provide a negative nitrogen balance.

In the latter connection it is important to emphasize that one cannot maintain normal human subjects on a program that will produce a prolonged positive nitrogen balance, because their body size components will not permit unlimited nitrogen loading if they start at a body size that is determined by exercise and genetics. Nonetheless, normal persons can be placed in positive transient nitrogen balance as was the case here. The statistical examination of the differences with amino acids alone as compared with those using added glucose, demonstrate a clear difference at both dose levels of glucose, with a marked improvement in nitrogen economy in both.

Ketone development is inhibited immediately by any amount of glucose given. The concept that ketosis is somehow favorable to nitrogen economy finds no basis in these experiments. At the low dose of glucose, insulin concentrations are not markedly elevated but nitrogen economy is markedly improved indicating that the availability of carbon chains for oxidation apparently improves nitrogen economy even though there is no stimulation to insulin production.

At the higher glucose dosage, the hormone results are quite remarkable. Insulin is now seen to be remarkably stimulated, rising to about five times its resting value. The glucagon level is dramatically inhibited to the lowest concentrations that we have seen in this laboratory with this endocrine setting, negative nitrogen economy disappears and a strongly positive balance is produced.

These data will be published in "Annals of Surgery"in Autumn 1977.
It would appear to be a clear demonstration of the need for a "balanced diet" in intravenous feeding and of the fact that carbohydrate, rather than having a deleterious action, has a remarkably favorable effect on nitrogen economy in intravenous feedings.

In addition, in the study of two surgical patients both chronically starving,the same glucose effect was clearly demonstrated with a marked improvement in nitrogen economy with added carbohydrate. In one of the starving patients the utilization of amino acids alone was better than it was in the normal.

4. Glycerol and Fat

Three years ago our laboratory reported (Brennan) that an amount of glycerol equivalent to that contained in the intralipid infusion had a marked effect on protein sparing. This three carbon carbohydrate (sometimes referred to as three carbon alcohol) is added to the infusion to make it isotonic. The molecule is both lipid soluble and water soluble. On a weight-for-weight basis, it is at least equivalent to glucose in its protein sparing effect. This suggests that the glycerol component of intralipid infusions is not to be neglected in the metabolic study of intravenous fat. Intralipid infusions contain added glycerol as well as that made available by the hydrolosis of the triglycerides. Our findings did not suggest nor did we ever propose that glycerol should be used clinically. Rather, this was a research demonstration that a small molecular weight carbohydrate - alcohol with unusual water-solubility properties, could be used as an energy source. Entirely free of nitrogen and devoid of any effect of insulin or glucagon concentrations, it nonetheless had a marked effect on protein sparing in man.

We can now report that glycerol given with the amino acid infusions has the same effect. Namely, that it improves the utilization of intravenously provided amino acids just as it

spares nitrogen in normal fasting man.

We have proceeded on now to the intralipid studies with amino acids and the findings are quite unexpected. From some reports in the older literature one would have predicted that fatty acid infusion would have little effect on nitrogen economy because fatty acids cannot be interconverted either into carbohydrate or into amino acids. In addition, interpretation of the intralipid experiments require the prior data on glycerol so as to control our or factor out the glycerol component into the intralipid infusions.

Our findings show that the intralipid infusion has a clearly increased nitrogen sparing and protein anabolizing effect over and beyond that observed with the glycerol contained or released in the infusion. The intralipid infusion is accompanied by a very mild ketosis, mild in all likelihood because of the fact that the glycerol present inhibits ketone formation. Fatty acid levels in the plasma are of course increased and triglyceride levels are very high. There is no stimulus to an increased insulin concentration. We have here therefore an additional evidence that the provision of energy sources can stimulate and improve nitrogen economy in man without the necessary intermediacy either of glucagon inhibition or insulin stimulation.

The amino acid results from these experiments are still being analyzed and have not yet been returned.

These findings likewise provide no support for the concept that muscle anabolism is somehow conducted at the expense of synthesis of visceral or acute phase proteins.

II. BRANCH CHAIN AMINO ACIDS

As indicated in the Application last year we undertook the study of branch chain amino acids in animals. The human studies are supported by the public health service and will be reported elsewhere, though mentioned briefly here because of their interest in trauma metabolism.

In animals branch chain amino acids given intravenously alone do not seem to have any remarkably adverse effect from toxicity point of view save, in dogs, for a rather brisk rise in serum uric acid concentration.

Infusion used was one prepared for us by Vitrum, Inc. in Sweden. Elaborate precautions in preparations and documentation of toxicity was required for its FDA approval in this country. It is important to note that our particular intravenous solution of branch chain amino acids has received full approval by the federal drug administration.

Experiments in man (supported from other research funding sources) has now been completed and demonstrates that the material does not have any remarkably adverse metabolic effect in man but does have a mild hyperurecemic effect, as well as that of acute hyperglycemia in some instances. The latter effect requires further elucidation. Infusion of the branch chain amino acids alone does not provide any remarkable stimulus to protein synthesis.

III. GLUCOSE COMPOSITION STUDIES USING TRITIATED GLUCOSE

During this past year it was the special project of Dr. Peter Wright to conduct a series of experiments in which tritiated glucose was used as a tracer for glucose. Without going into details here it appears that the tritiated glucose is an almost ideal tagged entity for use in man. It has many advantages. It is easy to prepare and count. The tritium is never recycled into glucose. Once the glucose is oxidized the tritium appears in body water. By estimates of body water it is possible to estimate the total rate of glucose oxidation. Our laboratory is well set up for the radioactive mesurements of tritium. The experiments can be conducted in only a few hours and the results are clearly reproducible.

These experiments have been completed and are now being prepared in manuscript form.

They show that the glucose turnover rate (K value or per cent turnover per time) as measureed by the single exponential decay curve of tritium, are remarkably constant in a whole variety of circumstances. Pool sizes however vary remarkably being elevated by glucagon and by the provision of glucose and remarkably so by insulin. Therefore the absolute replacement rate (i.e. the exponential decay expressed as grams per unit time) shows marked variability. The amount of body water available for glucose solution likewise shows variability linear with the pool size. It is notable that insulin alone of all the substances tested has an effect on the fractional turnover rate or K value and demonstrates remarkable increase in the volume of body water involved for glucose solution.

These studies have also been completed in a series of burn patients who demonstrate an increase in pool size and body water glucose space without any change in turnover rate (K).

Although these experiments have been completed at the present time, we do not plan to continue them again this coming year. Doctor Wright will carry on the methods in his new laboratories.

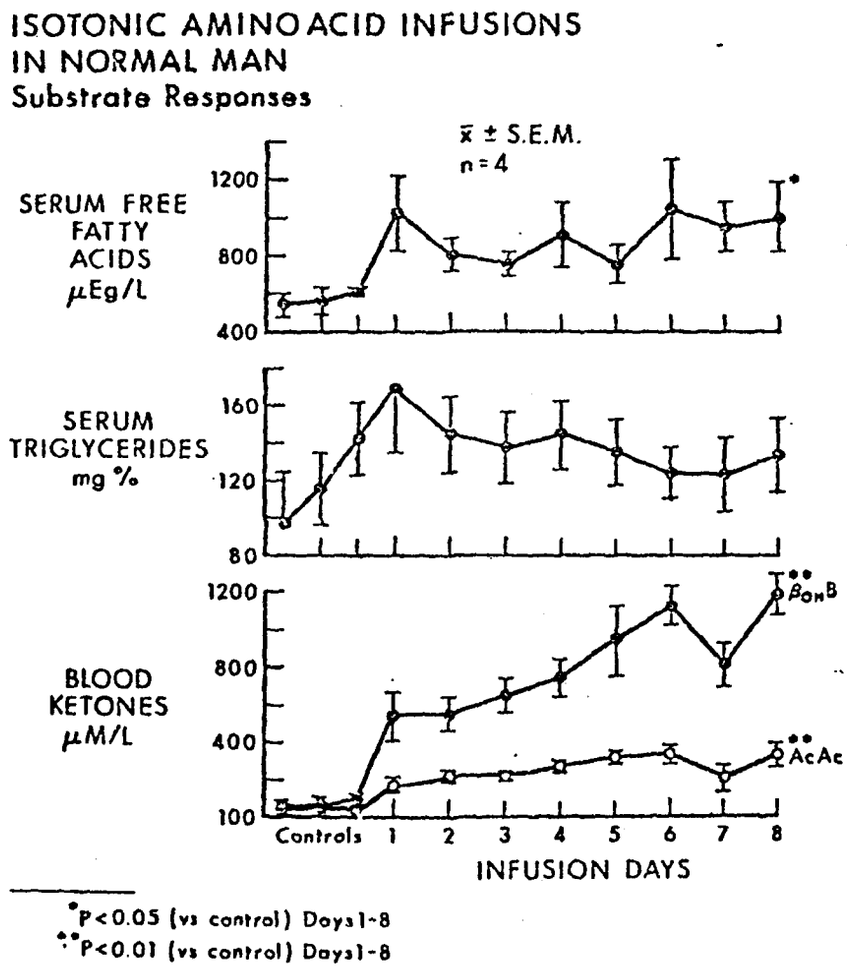
IV. MISCELLANEOUS

The multiple hormone infusion experiments referred to last year have been completed by Dr. Gary Fitzpatrick and are currently being written up for publication.

The most important finding is that no combination of catabolic hormones can produce as brisk a change in nitrogen metabolism as is observed after injury in man.

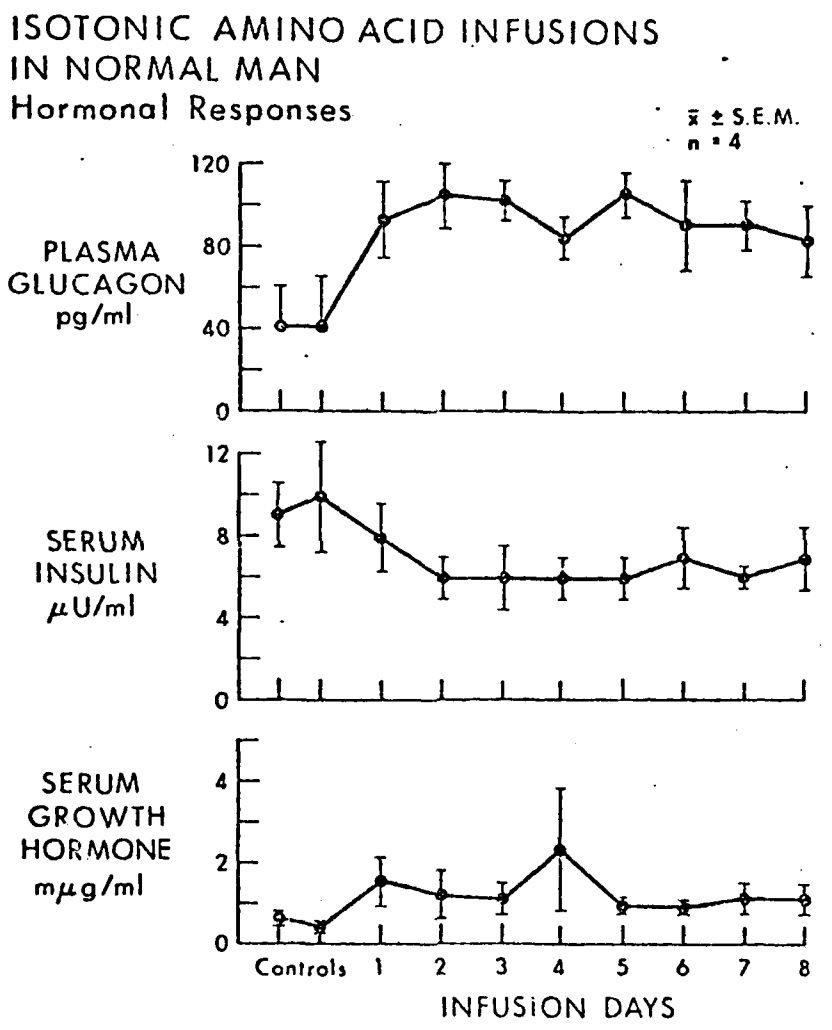
Glucagon hastens the "cleanup" of available low molecular weight nitrogen compounds, with increased ureagenesis and gluconeogenesis. But it does not appear to favor the hyrolysis of new protein and muscle.

Studies, in the rat, reconfirming the validity of the body water method using tritium, have been completed by Dr. Jesus Culebras and are currently being published in the Journal of Applied Physiology.



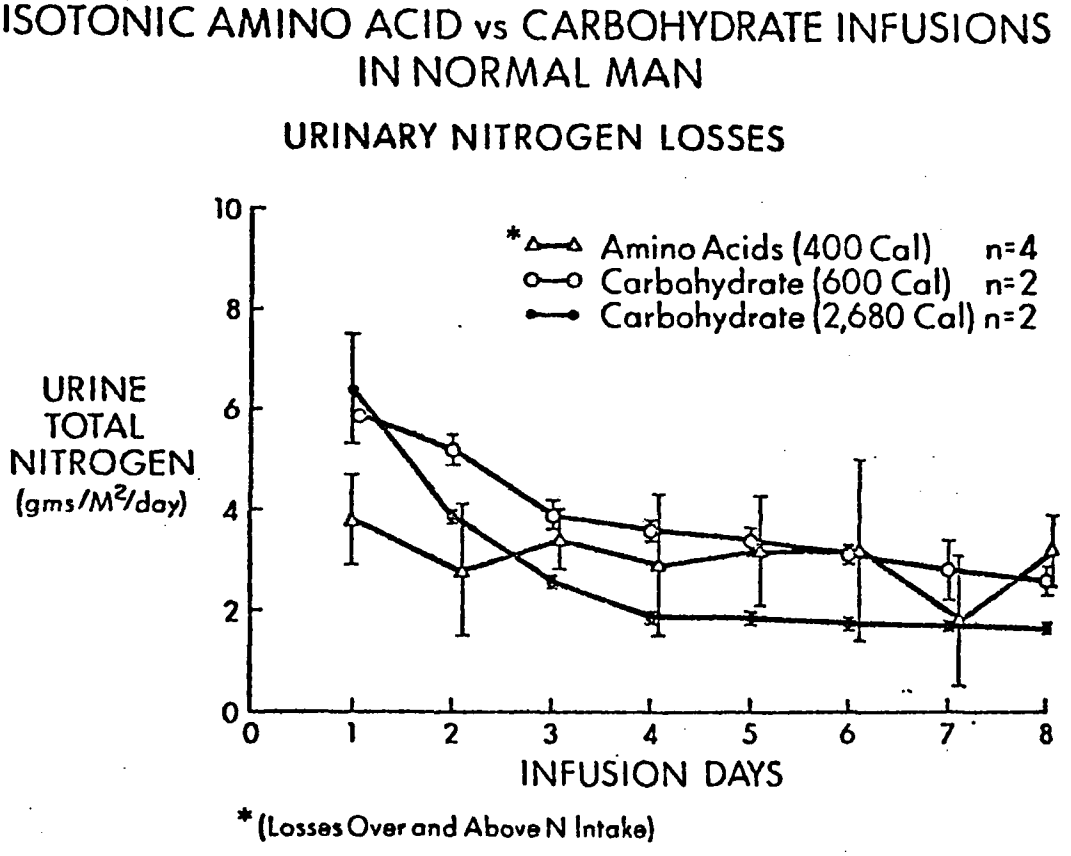
Amino Acids as the Sole Substrate. Triglycerides and ketones are stimulated. Fatty acids remain slightly elevated.

Figure 5



Amino Acids as the Sole Substrate. Glucagon is stimulated, insulin remains in the low normal range.

Figure 6



Amino Acids Compared to Carbohydrate in Fasting Man. High dose carbohydrate reduces urine nitrogen loss to its minimum level. With amino acids plus carbohydrate (not shown here) a positive balance is obtained.

Figure 7

Table 1

	GROUP 1 AMINO ACIDS ALONE				GROUP 2 AMINO ACIDS + GLUCOSE			
	CONTROL	N	INFUSION	N	CONTROL	N	INFUSION	N
Plasma glucose, mg/100 ml	93 ± 4	11	82 ± 4	32	94 ± 5	12	93 ± 4 *	32
Serum urea N, mg/100 ml	16 ± 5	11	20 ± 3	32	14 ± 3	12	16 ± 2 *	32
Blood alanine, μM/liter	290 ± 60	11	300 ± 49	32	328 ± 51	12	363 ± 40 *	32
Serum free fatty acids, μEq/liter	569 ± 99	10	897 ± 289	31	524 ± 178	12	415 ± 152 *	32
Blood ketones, μM/liter Day 1	109 ± 65	11	713 ± 312	4	116 ± 103	4	70 ± 23 *	4
Day 8			1,520 ± 333	4			187 ± 70 *	4
Serum insulin, μU/ml	10 ± 4	8	6 ± 2	32	6 ± 3	12	5 ± 2	32
Plasma glucagon, pg/ml	40 ± 41	8	94 ± 28	32	45 ± 17	12	64 ± 30 *	32
Urine urea N, gm/sq m/day			8.8 ± 1.3	32			7.3 ± 1.3 *	32
N balance gm/sq m/day			−3.0 ± 0.2	32			−0.9 ± 1.0 *	32

* $P < .01$ vs group 1 infusion (Student's t test).

Effect of Glucose on Amino Acid Utilization. Improved nitrogen economy, as measured by balance, is achieved with added glucose. A number of other changes are seen: lower ketones, elevated alanine, and less glucagon stimulation. Insulin is unchanged.

DAY	NITROGEN BALANCE gm/m^2/day		CUMMULATIVE N BALANCE gm/m^2/day	
	L*	H**	L	H
Infusion				
1	+0.28+0.88	+0.8+	+0.28+0.88	+0.8+
2	-0.99+0.69	+1.1+	-0.72+1.57	+1.9+
3	-0.88+0.79	+0.9+	-1.60+1.82	+2.8+
4	-1.33+0.91	+0.7+	-2.72+2.05	+3.5+
5	-0.43+1.15	0+	-3.15+1.73	+3.5+
6	-1.33+0.78	+0.6+	-4.48+2.34	+4.1+
7	-1.34+1.09	-0.1+	-5.81+3.35	+4.0+
8	-1.10+1.21	-0.6+	-6.16+5.20	+3.4+

All values are mean + SD

* L = Amino acids + 150 gm. glucose

** H = Amino acids + 600 gm. glucose

Nitrogen Balance With Amino Acids and Added Glucose at High and Low Dose. The effect of added carbohydrate is more marked at the higher dose level.

BLOOD HORMONE RESPONSE

DAY	INSULIN μU/ml		GLUCAGON pg/ml	
	L*	H**	L	H
Control				
-3	5.6+1	7.0+3	49+22	29+16
-2	6.5+4	7.0+2	43+17	40+13
-1	5.7+1	7.0+2	41+16	20+16
Infusion				
1	8.0+2	43+26	72+30	16+12
2	6.0+2	38+10	65+24	19+21
3	4.5+1	41+26	59+29	27+18
4	5.3+2	43+6	57+27	34+23
5	6.3+2	43+13	65+30	34+13
6	5.5+3	46+17	55+22	37+25
7	4.3+2	45+14	62+29	23+14
8	4.0+1	30+13	81+59	41+28

All values are mean + SD n=4

* L = Amino acids + 150 gm. glucose

**H = Amino acids + 600 gm. glucose

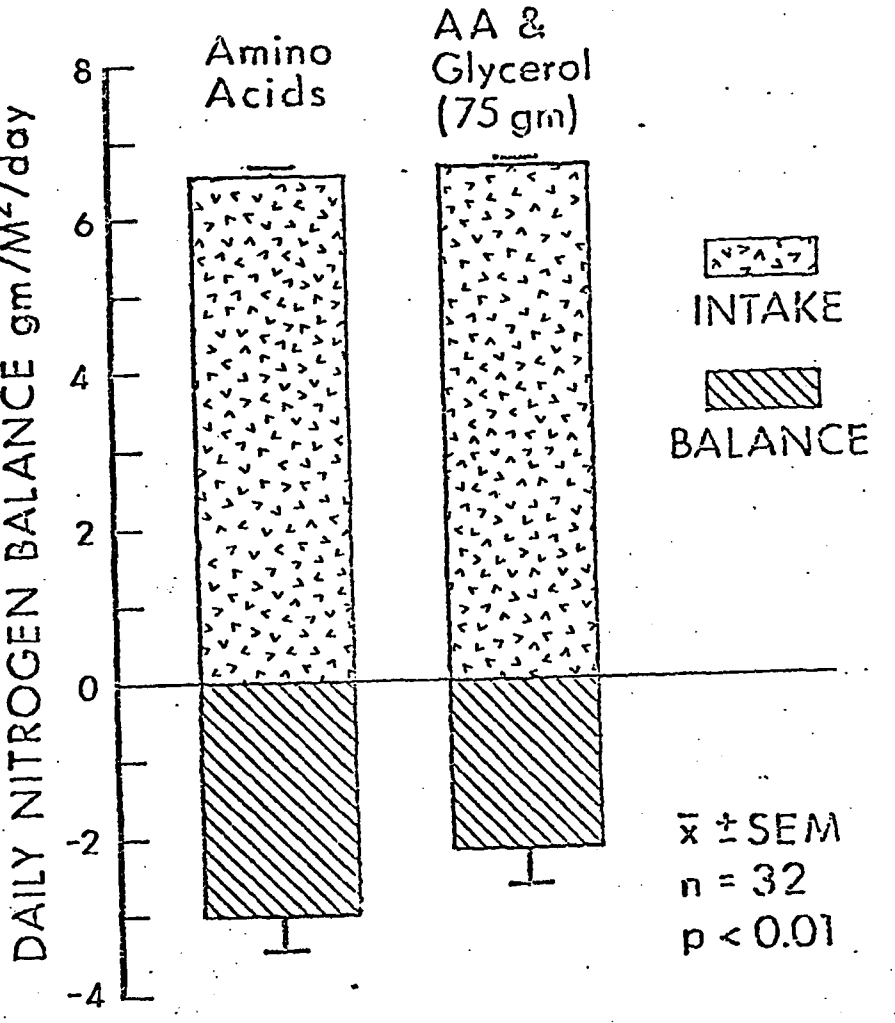
Hormone Responses to Amino Acids With Added Glucose at High and Low Dose. With high dose (but not at low dose) glucose, insulin is stimulated and glucagon suppressed. There is improved nitrogen economy at both dose levels, suggesting that endocrine response alone, is determining in protein economy.

Table 1[1]

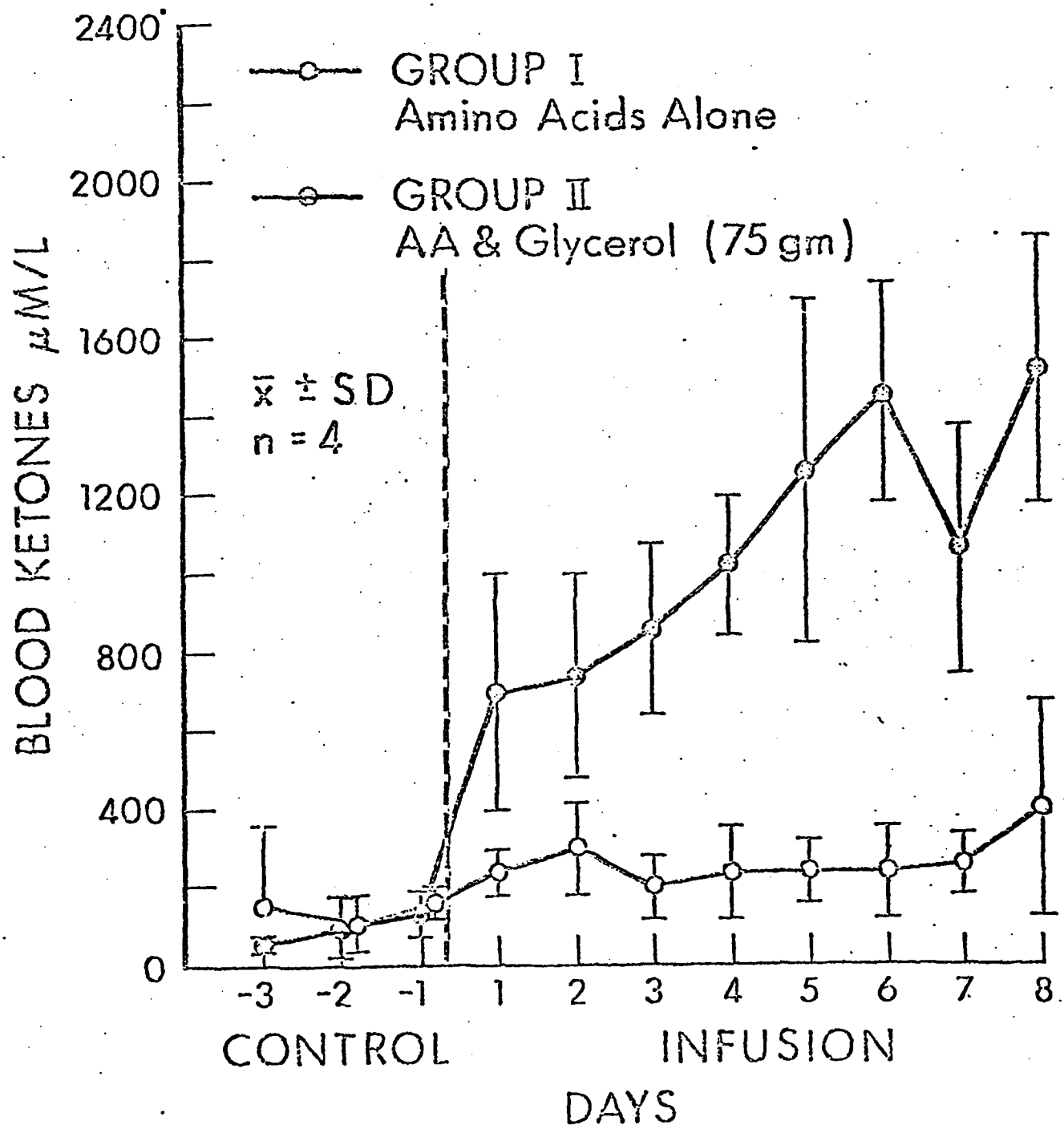
	GROUP 1 AMINO ACIDS ALONE		GROUP 2 AMINO ACIDS + GLYCEROL	
	CONTROL (MEAN ± SD)	INFUSION (MEAN ± SD)	CONTROL (MEAN ± SD)	INFUSION (MEAN ± SD)
Plasma glucose, mg/100 ml	93 ± 4 (11)	82 ± 4 (32)	94 ± 4 (11)	89 ± 4* (32)
Blood alanine, mM/liter	0.29 ± 0.06 (11)	0.30 ± 0.05 (32)	0.33 ± 0.07 (11)	0.36 ± 0.04* (32)
BUN, mg/100 ml	16 ± 5 (11)	20 ± 3 (32)	13 ± 2 (11)	15 ± 2* (32)
Blood ketones, μM/liter	109 ± 65 (11)	1,081 ± 394 (32)	142 ± 97 (11)	266 ± 134* (32)
Serum FFA, μEq/liter	569 ± 99 (10)	897 ± 289 (31)	483 ± 99 (11)	543 ± 137* (32)
Serum TG, mg/100 ml	118 ± 41 (10)	138 ± 37 (31)	78 ± 24 (10)	89 ± 20* (32)
Serum glycerol, mg/100 ml	. . .	. . .	0.8 ± 0.3 (10)	2.5 ± 0.6 (32)
Serum IRI, μU/ml	10 ± 4 (8)	6 ± 2 (32)	6 ± 2 (11)	5 ± 2 (32)
Plasma IRG, pg/ml	40 ± 41 (8)	94 ± 28 (32)	62 ± 31 (11)	111 ± 38 (32)
Cumulative UUN excretion, gm/sq m	. . .	71.3 ± 6.8 (32)	. . .	56.2 ± 5.5* (32)
Cumulative urine NH_3 N excretion, gm/sq m	. . .	7.4 ± 0.8 (32)	. . .	5.4 ± 0.5* (32)
Nitrogen balance, gm/sq m/day	. . .	−3.03 ± 1 (32)	. . .	−2.2 ± 1* (32)

[1] BUN, blood urea nitrogen; FFA, free fatty acids; TG, triglycerides; IRI, immune reactive insulin; IRG, immune reactive glucagon; UUN, urine urea nitrogen excretion. Numbers in parentheses indicate number of volunteer days.
* $P < .01$ vs group 1 (infusion).

Glycerol as a 3-Carbon Energy Source: Effect on Amino Acid Utilization. The effects on ketones, fatty acids and nitrogen balance, are especially prominent. There is no stimulation of insulin.



Glycerol Effects. The improvement in nitrogen economy is significant but clinically marginal.



Glycerol Effects on Amino Acid Utilization.
The lowering of ketones (shown here) is accompanied by a clear improvement in nitrogen economy.

	n	serum glucose mg/dl	exchangeable glucose mass mg/kg	glucose replacement rate mg/kg/min	estimated glucose space ml/kg	K
Control	13	85.2 ± 6.4	209.1 ± 35.8	2.20 ± 0.37	244.5 ± 32.0	1.03 ± 0.17
Acute burns	5	119.6 ± 17.7	323.3 ± 81.1	3.59 ± 0.72	263.9 ± 32.9	1.13 ± 0.14
t-test P=		<0.00001	<0.001	<0.00005	<0.03	<0.03

TABLE I

Tritiated Glucose Dynamics in Burns. Exchangeable glucose, replacement rate and "k" value (fractional turnover rate) are increased, as is the plasma glucose.

	n	serum glucose mg/dl	exchangeable glucose mass mg/kg	glucose replacement rate mg/kg/min	estimated glucose space ml/kg	K
Control	13	85.2 ± 6.4	209.1 ± 35.8	2.20 ± 0.37	244.5 ± 32.0	1.03 ± 0.17
3 week burns	4	102.0 ± 18.3	365.5 ± 78.3	5.03 ± 2.00	351.4 ± 123.3	1.31 ± 0.33
P=		<0.1	<0.0001	<0.0001	>0.1	>0.1

TABLE II

Tritiated Glucose in Burns. Even at 3 weeks there are clear changes in glucose kinetics. Insulin (not shown here) is now appropriately elevated whereas, in the acute burn, it is anomolously suppressed while glucose is elevated.

UNITED STATES ARMY - RESEARCH AND DEVELOPMENT COMMAND
Department of Surgery of the Harvard Medical School
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Dr. Francis D. Moore

PROGRESS REPORT - 1975-1976

The work described in this section of the report is under the direction of Dr. Nicholas O'Connor.

Bacterial Endocarditis

Since its introduction in 1970, the flow-directed balloon-tipped catheter has been widely used in monitoring the circulatory hemodynamics of critically ill patients, including burn patients. A review of six consecutive burn patients who had been monitored with a pulmonary artery catheter, and who later died of their injury, showed that 4 of the 6 had aseptic right sided endocardial lesions at autopsy, and the other 2 had right-sided bacterial endocarditis. This review prompted a study of the development of right sided endocardial lesions in dogs with indwelling pulmonary artery catheters. A copy of this recently submitted manuscript is enclosed.

Dogs were anesthetized, No. 7 French Swan-Ganz thermodilution catheters were inserted into the external jugular vein, and directed into the pulmonary artery. The end of the catheter was cut off at the venous cutdown site, and the skin closed, so the end of the catheter was buried subcutaneously. The dogs were sacraficed at 1, 3, 5, 7, 10, 12 and 14 days following insertion and their hearts examined. All the dogs showed non-bacterial thrombotic endocardial lesions of the superior vena cava, right atrium, tricuspid valve, right ventricle, and pulmonic valve. One each of the 7 and 12 day dogs developed abscesses at their venous cutdown sites and had acute bacterial endocarditis of the tricuspid and pulmonic valves. Two dogs had their catheters removed after 5 days and were sacrificed 2 weeks later. Examination of their hearts revealed endocaridal lesions which were well organized with marked fibrosis.

This study demonstrates that the constant pumping action of the heart against a stiff indwelling catheter can easily traumatize the endocardium or endothelium of a vessel. The resultant thrombotic lesions can easily become infected leading to acute bacterial endocarditis. These non-bacterial lesions organize quickly and are well on their way to healing in 3 weeks.

Plans For The Coming Year

The bacteria recovered from the infected endocardial lesions were alpha hemolytic streptococci. Attempts to infect the non-bacterial thrombotic lesion with various staphylococci strains were unsuccessful.

PROGRESS REPORT - 1975-1976

In this coming year a series of dogs will have the catheters inserted and left in place for 7 days. Forty-eight hours following removal of the catheters, the dogs will be infused with alpha hemolytic streptococci to see if bacterial endocarditis can be induced when the catheters are no longer in situ.

Pulmonary Studies In Thermal Injuries

Acute, thermally injured casualties frequently develop early respiratory problems. These problems are especially severe if there has been an inhalation component with the thermal injury.

Chinard first introduced the concept of the double indicator-dilution method for the estimation of pulmonary extravascular water volume (PEWV). This laboratory applied the method to clinical studies in patients. The method involves the simultaneous injection of two indicators into the right atrium. One of the indicators, usually Evans blue dye or I^{131} albumin, is an intravascular, nondiffusible indicator. The other indicator, tritiated water, is rapidly diffusible and in a single pass through the pulmonary circulation exchanges with most of the water present in the lungs. After their passage through the lungs dilution curves of the two indicators are measured by arterial sampling. Mean transit time differences for the two curves multiplied by cardiac output yields a value which can be considered the differences of the two central volumes, one including PEWV, the other excluding it.

PEWV measurements by this technique have certain disadvantages. Repeatability is severely limited by the large sampling volume required, the background buildup of dye, and isotope dosimetry. Sample processing requires multiple pipettings of samples, colorimetry, and isotope counting; results are delayed for days. Finally in validation experiments done in animals, the method measures only 60-70% of lung water measured gravimetrically at autopsy. Noble introduced the use of alternative indicators that are detectable by transducers: sodium as the intravascular one and a thermal pulse as the diffusible or extravascular one.

We developed an instream monitoring catheter that can be substituted for the peripheral arterial line commonly used in critically ill patients and which detects the indicators used in the modified double indicator method. It is a 5-French catheter, with a lumen for pressure measurement and blood sampling; the tip carries a thermistor to measure temperature and a pair of ring electrodes to sense changes in sodium concentration. The determination of PEWV by the sodium and thermal indicators has been designated as lung thermal volume (LTV). In practice, the measurement requires the insertion of a central venous line and the special arterial line. The indicator combination is room temperature saline, and can be used repetitively. Since the indicator concentrations are determined *in vivo* by the catheter, no blood sampling is required, and the results

are immediately available with the use of computers. Validation experiments carried out in animals have shown LTV to be a reasonable precise estimate of the amount of water in the lung determined by gravimetric methods.

Over the past year several observational studies of acute thermally injured patients have been carried out. These studies demonstrate a very early and sometimes prolonged increases in LTV (fig.). If there has been no concomitant inhalation injury, the early rise in LTV quickly abates after the initial fluid resuscitation. These increases in LTV without concomitant increases in left heart filling pressures essentially characterize these increases to be classified as low pressure pulmonary edema.

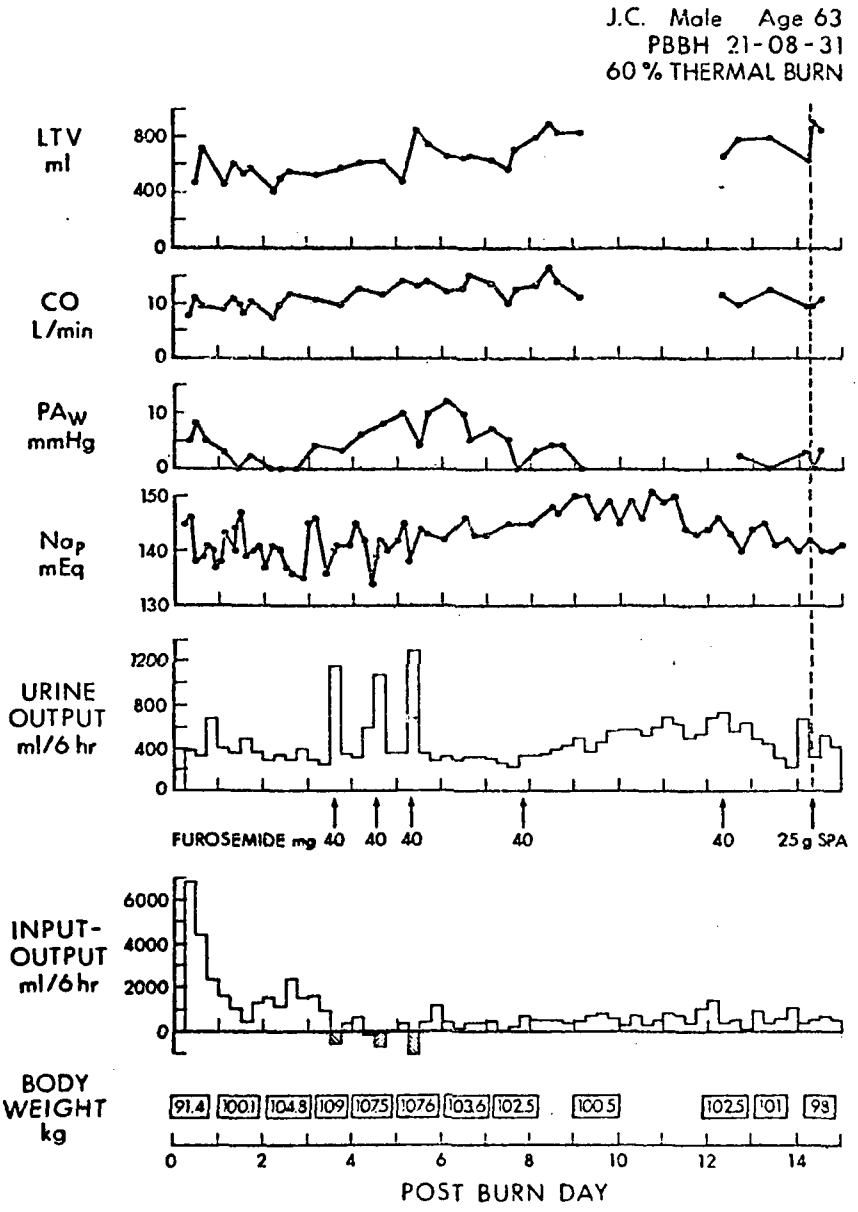
Several studies from these laboratories have demonstrated that positive end expiratory pressure decreases the accumulation of water in the lungs in dogs with low pressure edema. The mechanism by which airway pressure relates to extravascular water, is however poorly understood.

The long term effects of inhalation injury in burn victims is not well documented. Studies of firemen who are subject to smoke inhalation as part of their work have shown a more rapid deterioration of their pulmonary function studies over time when compared to a comparable group of controls. This deterioration was most marked in studies of their vital capacity.

Plans For The Coming Year

1. Animal Studies

A series of animal studies is proposed to try to elucidate the mechanism of interaction between airway pressures and pulmonary extravascular water. In this study dogs will be anesthetized and endotracheally intubated. A central venous catheter, pulmonary artery catheter, and an intra-aortic LTV catheter will be inserted. Airway pressures will be varied in two ways. Firstly, a positive airway pressure will be applied for short (30 sec) periods of time. The pressure will be raised by intervals of 5 cm H_2O from 0 to 50. Secondly, a negative pressure will be applied to the thorax with the dog in a body box. The pressure will be lowered by intervals of 5 cm H_2O from 0 to 50 over short time periods. The effects of these pressure changes on pulmonary artery pressure, pulmonary artery wedge pressure, airway pressure, cardiac output and LTV will be measured.


J.C. Male Age 63
PBBH 21-08-31
60 % THERMAL BURN
LTV ml
800
400
0
CO L/min
10
0
PAW mmHg
10
0
NaP mEq
150
140
130
URINE OUTPUT ml/6 hr
1200
800
400
0
FUROSEMIDE mg 40 40 40 40 40 25 g SPA
INPUT-OUTPUT ml/6 hr
6000
4000
2000
0
BODY WEIGHT kg
91.4 100.1 104.8 109 107.5 107.6 103.6 102.5 100.5 102.5 101 98
0 2 4 6 8 10 12 14
POST BURN DAY

ABSTRACT

The postmortem finding of acute right-sided bacterial endocarditis in a burn patient monitored with an indwelling pulmonary artery (Swan-Ganz) catheter for 14 days prompted a review of burn autopsies in which the catheter had been used. Autopsies of six consecutive burn patients monitored with a pulmonary artery catheter showed septic or aseptic endocarditis. In two of the six patients, right-sided staphylococcal endocarditis was the anatomic cause of death. In the remaining four patients, the lesions were aseptic thrombotic vegetations involving primarily the right atrium, tricuspid valve, right ventricle and pulmonic valve. Histologically, the degree of organization of these aseptic thrombi corresponded to the time interval between insertion of the catheter and death of the patient.

Several factors in the severely burned patient would favor endocarditis where a foreign object impacts on the heart valves. These include intermittent bacteremia, hypercoagulability, hyperdynamic cardiovascular function, and the use of antibiotics resulting

in resistant strains. While the Swan-Ganz catheter or an indwelling pulmonary artery catheter can provide useful monitoring information, it is sometimes responsible for serious complications in the burned or septic patient.

INTRODUCTION

Since its introduction in 1970, the flow-directed balloon-tipped pulmonary artery catheter (Swan-Ganz catheter) has been widely used in monitoring the circulatory hemodynamics of critically ill patients.[1] There are now several reports of complications associated with the catheter including intracardiac knotting, perforation of the pulmonary artery, fatal pulmonary hemorrhage, endothelial damage with overlying thrombus in a pulmonary artery with subsequent embolism and infarction, pulmonary ischemic lesions due to wedging of the catheter tip, and aseptic thrombotic endocarditis.[2-7] A recent study has shown that Swan-Ganz catheterization increases the incidence of aseptic thrombotic endocarditis,[8] and the first case of septic endocarditis associated with a pulmonary artery catheter has been reported by Greene et al.[9]

The observation, at autopsy, of acute right-sided bacterial endocarditis in a burn patient monitored with an indwelling pulmonary artery catheter for 14 days prompted a review of the autopsies of six consecutive burn patients, who had a Swan-Ganz catheter.

MATERIAL AND METHODS

From March, 1974 to February, 1975, six burn patients, who had been initially monitored with an indwelling pulmonary artery catheter (7 Fr. Swan-Ganz thermodilution catheter) and succumbed, had unrestricted postmortem examinations. Retrospectively, the patients' charts, autopsy summaries, available gross organs including all six hearts, and microscopic slides were reviewed. In these patients, the catheters were inserted through antecubital venous cutdown sites made in unburned skin or in fresh burn eschar. The catheter tip was placed in a position in which wedge pressures were obtained when the balloon was inflated, and the catheters remained in place for periods of up to 14 days. All six patients received essentially the same burn care.

RESULTS

At autopsy, all six burn patients who had an indwelling pulmonary artery catheter showed septic (two patients) or aseptic (four patients) endocardial lesions in the right heart. Table 1 summarizes the pertinent data in each case. In cases 3 and 6 where septic endocardial lesions were found, the anatomic cause of death was the result of bacterial endocarditis.

In case 3, a pulmonary artery catheter was inserted four hours after the burn injury. Three catheter changes were made over the next 13 days through the same insertion site, and the catheter was removed on the fourteenth post burn day (PBD). On PBD 5, there were two positive blood cultures for Enterobacter cloacae, and on PBD 13, blood cultures grew Enterobacter cloacae and Staphylococcus aureus. On PBD 14, the catheter was removed. During the next ten days, the major clinical problem was bradycardia with nodal rhythms and premature ventricular contractions, and the patient died on PBD 24. Postmortem examination revealed severe bacterial endocarditis of the tricuspid and pulmonic valves, organized thrombi of the right atrium and ventricle, and an organizing myocardial abscess (2 cm) in the posterolateral left

ventricular wall. The endocardial vegetations, right atrial thrombi, and myocardial abscess showed Gram positive cocci. Septic emboli were found in the lungs and kidneys.

In case 6, a pulmonary artery catheter was inserted shortly after the burn injury and left in place until PBD 4, when it was withdrawn into the right atrium and used as a central venous pressure (CVP) line. This catheter was discontinued on PBD 7, and thereafter numerous CVP lines were placed over the following 108 days. The tips of any of these CVP lines could have extended to the level of the tricuspid valve. The initial burn injury resulted from a suicide attempt. The patient continually mutilated his split thickness skin grafts and developed repetitive staphylococcal sepsis due to the difficulty in maintaining coverage of the burn site. On PBD 115, the patient had a sudden respiratory arrest. Resuscitation was unsuccessful. Postmortem examination revealed large septic thrombi on the leaflets of the tricuspid valve with the largest thrombus measuring 4.0 x 3.5 x 2.0 cm. The tricuspid leaflets were histologically normal showing only minimal reaction to the attached thrombi. The thrombi showed layers of old organized areas through organizing areas to superficial layers of recent thrombosis. Each thrombus contained large colonies of Gram positive cocci. The lungs showed a recent septic embolism to the

major pulmonary artery of the right lower lobe and multiple septic emboli to smaller pulmonary artery branches in both lungs. The embolic material was histologically identical to the septic thrombi on the tricuspid valve, containing colonies of Gram positive cocci. The immediate anatomic cause of death was septic pulmonary embolism.

In the remaining patients (1,2,4 and 5), aseptic thrombotic endocardial lesions involved variously the right atrium, tricuspid valve, right ventricle, and pulmonic valve. Only in case 1 were endocardial lesions also found in the left heart. These were small aseptic thrombotic vegetations on the mitral and aortic valves which showed the changes of old, healed rheumatic valvulitis. In patients 2, 4, and 5, the endocardial lesions were thin layers of aseptic thrombus in variable stages of organization. Histologically, the degree of organization of the thrombi in each case corresponded to the time interval between insertions of the catheter and death.

DISCUSSION

Adverse reactions to procedures commonly employed in the care of the critically ill, should be reported in the literature. Such enables other physicians to take

appropriate or judicious precautions even though an episodic or anecdotal report of this type gives no idea of overall incidence.

The initial stimulus for development of the pulmonary artery catheter was the need for accurate central pressure monitoring in seriously ill patients.[10] Swan and Ganz reported its use in cardiac and noncardiac conditions including sepsis[1], and its use in acute management of ten burn patients has been reported without serious complications.[11] The circulatory system of the burn patient undergoes rapid fluid shifts and accurate fluid-volume control is essential during the period of resuscitation. Furthermore, the measurement of thermal dilution cardiac output with the catheter is useful in monitoring the high cardiac output states seen in thermal injury and the cardiac response to large volumes of fluid administration. For these reasons, it was felt to be clinically important to use the pulmonary artery catheter in the initial treatment of these six burn patients. The postmortem findings of septic or aseptic endocardial lesions in all six cases, however, may suggest that the catheter should not be used in burn patients.

As suggested by other authors[5,7], the constant pumping action of the heart against an indwelling catheter can easily traumatize the endocardium or endothelium of a vessel. The burn patient may be more susceptible to this endocardial trauma because of the hyperdynamic cardiac state seen with early burn injury. In addition, recent investigations of the rheological and hematologic changes in the postburn period show that blood viscosity rises acutely and remains elevated for four to five days, the platelet count rises slowly and remains elevated for weeks, platelet adhesiveness is increased, and the probable release of coagulation factors from the burn area promotes in vivo hypercoagulability.[12] The combination of endothelial injury and hypercoagulability of blood may promote the formation of thrombotic vegetations. These vegetations could then easily become a nidus for bacterial colonization, as the burn patient experienced bacteremias, with the subsequent development of bacterial endocarditis.

In addition to the Swan-Ganz catheter, a special indwelling triple lumen thermistor device is sometime used for repeated cardiac output measurements by thermodilution.[13] Where patients are septic, prone to thrombosis, or subject

to intermittent bacteremia, similar intracardiac lesions could result from such indwelling sensors.

Therefore, although the pulmonary artery catheter is useful in accurate fluid-volume control in burn patients and other septic patients, the complications associated with it are extremely serious and must be weighed against its use in such patients. Our present policy is to use central venous pressure monitoring with radiologic localization of the tip well above the right atrium; where the pulmonary artery position is mandated by clinical circumstances we advise removal within 24 hours.

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Table 1. Six Consecutive Burn Autopsies of Patients Monitored with an Indwelling Pulmonary Artery Catheter

CASE NO.	AGE	% BURN DEGREE	DEATH DATE (DAYS)	CAUSE OF DEATH	P.A.C. (LENGTH CATHETER IN)	ENDOCARDIAL LESIONS AT AUTOPSY
1	66	70% 2nd & 3rd	PBD 13	Respiratory Failure Bronchopneumonia	First 30 hours	NBTE* of TV, MV, and AV**
2	57	70% 3rd	PBD 29	Respiratory Failure Bronchopneumonia	First 7 days	NBTE of RA, TV, and PV
3	64	60% 3rd	PBD 24	Acute Bacterial Endocatditis of TV & PV with Myocardial Abscess	First 14 days	Acute Bacterial Endocarditis of RA, RV, TV, and PV
4	58	65% 2nd & 3rd	PBD 21	Gram Negative Sepsis	First 4 days	NBTE of RA, RV, and TV
5	45	75% 3rd	PBD 10	Respiratory Failure Severe Necrotizing Bronchopneumonia	First 5 days	NBTE of RA, TV, and PV
6	30	60% 2nd & 3rd	PB 115	Septic Pulmonary Emboli Bacterial Endocarditis of TV	First 4 days***	Bacterial Endocarditis of TV

Abbreviations: PBD postburn day, TV-tricuspid valve, MV-mitral valve, PV-pulmomic valve, AV-Aortic valve, RA-right atrium, RV-right ventricle

* NBTE (nonbacterial thrombotic endocarditis)
** Mitral and aortic valves showed old healed rheumatic valvulitis
*** On PBD 5, the PA line was withdrawn into the RA and used as a CVP line, then removed on PBD 7.

II COMPUTER STUDIES

The Development Of Mathematical Models Of Burn Fluid Pathophysiology

A Brief Background

With a major thermal injury there are severe dislocations of fluid and electrolyte pathophysiology. There are several lines of evidence to suggest that the quality of the resuscitation therapy has an influence on the number of complications and the final outcome of the patient. To confirm this, a retrospective review was performed on the data of patients treated on the Peter Bent Brigham Burn Service. Two reviewers independently rated the quality of fluid therapy and the overall course of the patient using simple objective scales. Analysis showed that the correlation of the two ratings was 0.38, and with age and percent burn held fixed, their partial correlation was 0.33. This result suggests that the better the quality of fluid therapy, the more likely a favorable course and outcome for the patient.

Having determined that the quality of fluid therapy is important, a selection of the varied fluid regimens must be made. All of the regimens have as their underlying objectives the maintenance of cardiac output, circulating blood volume and renal function to avoid the hazards of burn shock and renal failure. All these "budgets" are quite effective in avoiding these hazards. Yet, no significant randomized clinical trials have been performed comparing these various therapeutic modalities with each other, their effectiveness in avoiding early complications and their effect on the eventual outcome of the patients.

The rationale for continuing to develop mathematical models of the fluid and electrolyte dislocations that occur in a patient with thermal injury along with the patient's response to therapy rests on the ability to use the model to test out different strategies of fluid treatment. Furthermore the model should aid in the development of a treatment algorithm which is tailored more closely to individual patient constraints. Such an algorithm could then be programmed into a set of computerized instructions to guide the personnel caring for the patient.

B Description Of The Modelling Process

Box models are commonly used in symbolic and numeric representations of complicated processes which are simplified and articulated by the laws of conservation. Stocks and fluxes are connected to form a network in much the same way that a child's Tinker Toy is used to fashion complicated structures from a few basic components. Directed arrows represent flows of material (or fluxes) and boxes represent inventories (or stores). Planning the system includes specifying the capacity constraints on the fluxes and stores and then operating the system by making decisions (such as setting demands, establishing a price structure, specifying re-order points and operating rules for the stores, etc.). Thus operating the system is a less comprehensive enterprise than planning it; in clinical settings, we are limited to operating human systems whose characteristics are established by processes commonly beyond our control.

Some system operating characteristics lie outside our control, and some beyond our understanding. Introducing the same amount of fluid into two burn patients identical in all those respects which we perceive to be important will commonly produce a different hematocrit response in each, from which we conclude that we do not know enough about the process to write an unambiguous model with causal or explanatory richness adequate to reproduce the linkages. It is important to note that to be useful the model need not be causal in the sense that it is based on scientific axioms. In some instances perfectly acceptable associative models can be used to predict the performance of complicated systems without recourse to first principles.

However, in some cases the correlation among presumably independent predictor variables or arguments can lead to unsatisfactory results. Suppose we hypothesize the linear model

$$y = a_0 + a_1 x_1 + a_2 x_2 + \varepsilon$$

where x_1 and x_2 are correlated predictor variables, y is the predicted or output variable, the a_i are coefficients estimated by some algorithm such as OLS (ordinary least squares) and ε is a residual or error term. The a_i typically are estimated from simultaneous observations on the x_i and y. We do not include a second subscript on the x_i and y; it is understood that the observations comprise a sample of size n and that each of these observations consists of a triple $(x_1, x_2, y)_t$, with t = 1, 2,...,n. It is convenient to regard a_i as the incremental change in y given a unit change in x_i, and this interpretation would be appropriate if the x_i were mutually independent. But because in

We can now construct a box model for which the fluxes or arrows can be represented by functions of current and recent values of system state values, therapeutic inputs and random perturbations. The functional form of these fluxes represents the frontier of our understanding of the processes; in some instances they can be reduced to axiomatic statements or first principles, while in others they represent empirical association which might include significant random components.

The purpose of any such model is to gain enough insight into the prototype process to provide material assistance in meeting some objective. At the most fundamental level this objective is simply to understand the process, to identify parameters which characterize system response, to push the frontier of understanding. In these cases the criteria for accepting a model are based on unambiguous, repetitive agreement between prediction and performance. However, in a clinical setting the criteria are quite different; they are skewed toward selecting that model which, when used as a guide to therapy, gives "the best" results. This leads immediately to important questions: (i) How do we define a therapeutic result? (ii) If several components or characteristics define a result, how are they combined to allow nomination of one as being unambiguously better than any other? (iii) If therapeutic regimen R_i is associated with decision model M_i, and if R_i gives uniformly mediocre results over a large number of patients while R_j gives some outstanding results combined with some distressing ones, how can the model be assessed? That is, are there characteristics of the patient which would dictate that he belongs to that set of individuals for which model M_i or M_j would be appropriate?

APPENDIX

A Proposed Model

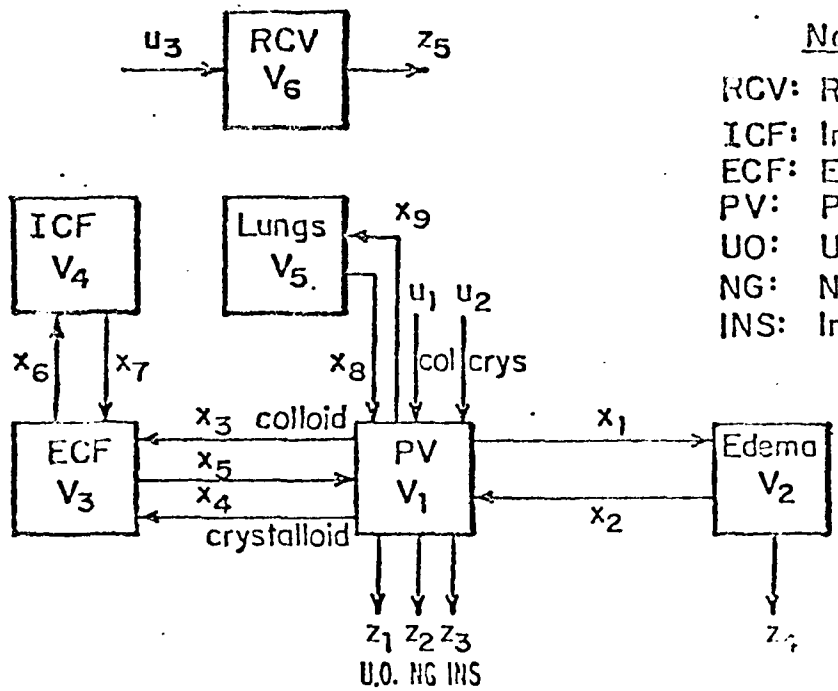
Figure 1 shows a proposed model of the fluid balance and management model for burns. It should be emphasized that the schematic diagram represents a simplistic model of a poorly understood system; thus the model may change on at least two accounts; (i) improved understanding of the system leading to consequent alterations of the model, and (ii) the need for more (or less) refinement in the model in order to render it consistent with available therepeutic options. Thus the work itself will help identify which model components must be elaborated, which additional ones should be included, and which might be deleted. In particular, the study of the system response, as reflected by the establishment of indices of the recovery course or trajectory, will help determine the final version of the model.

Nonetheless it is instructive to consider the general research strategy as if the postulated model were the final version.

The basic components of the model consist of storage elements, of directed flows among the elements and of inputs/outputs connecting the elements to the outside world. The state variables associated with each of the storages are the fluid volumes currently in storage and measures of the spaces within which the fluids are contained. The volumes change in accordance with a set of hypothesized differential equations, as functions of physiologic response and the pressures exerted by the fluids in their several compartments. The arguments and form of these differential equations characterize the limits of our knowledge of burn physiology, and it is proposed to fit these "technological functions" by retrospective examination of a large number of patient records.

That is, we posit functional relationships among the variables, [8] including transfers among the compartments and losses to the environment(leakage, urine, nasogastric and insensible losses, etc.) and by continuity we calculate plasma volume (PV). From the size of the patient we estimate red cell volume, whereupon the hematocrit can be calculated. Thus our model, although fundamentally a fluid budget or balance, becomes a model of hematocrit (or plasma volume); this is particularly useful because hematocrit observations are commonly available from patient records and thus justify a "best estimator" of the system on the assumption that the model contains all the relevant arguments, variables and functional relationships.

Figure 2 shows the notation for the vectors, state variables and inputs to the system. The inputs are basically the fluids administered, with the rate of administration being a matter of concern. Suppose the therapeutic regimen calls for administration



Notations

RCV: Red Cell Volume
ICF: Intracellular Fluid
ECF: Extracellular Fluid
PV: Plasma Volume
UO: Urine Output
NG: Naso-gastric Loss
INS: Insensible Loss

FIG. 1 SCHEMATIC DIAGRAM OF FLUID SYSTEM

FIG. 2

$$\dot{V}_1 = x_2 - x_1 - x_3 - x_4 + x_5 - x_9 + x_8 - z_1 - z_2 - z_3 + u_1 + u_2$$

$$\dot{V}_2 = x_1 - x_2 - z_4$$

$$\dot{V}_3 = x_4 + x_3 - x_5 + x_7 - x_6$$

$$\dot{V}_4 = x_6 - x_7$$

$$\dot{V}_5 = x_9 - x_8$$

$$\dot{V}_6 = u_3 - z_5$$

$$\dot{V}_1 + \dot{V}_2 + \dot{V}_3 + \dot{V}_4 + \dot{V}_5 + \dot{V}_6 = u_1 + u_2 + u_3 - z_1 - z_2 - z_3 - z_4 - z_5$$

Definition of Hematocrit

$$H = V_6 / (V_1 + V_6)$$

Variables

V_1: Plasma volume

V_2: Edema

V_3: Extra-cellular fluid

V_4: Intra-cellular fluid

V_5: Lung water

V_6: Red cell Volume

x's are transfers

z_1: Urine output

z_2: Naso-gastric loss

z_3: Insensible loss

z_4: Burn leakage

z_5: Red blood cell loss

u_1: Colloids in

u_2: Crystalloids in

u_3: Red cells in

H_i: hematocrit at time i as predicted by model

H_i^*: actual value (measured) at time i

$\sum_i (H_i - H_i^*)^2$ is a criterion function to be minimized

of one liter per hour. However, it might happen that the entire liter was administered in (say) 30 minutes so the body senses its entry at the effective rate of 2 liters per hour. This might cause circulatory perturbations and lead to subsequent difficulties. Thus the model's "administration" of fluids must be flexible in that it should represent not only the total volume in the time period but that various rates, and their potential consequences, should be modeled.

Part of the input to the model also describes the administration of drugs. For example, the model should reflect the fact that if urine output falls below threshold values, the patient is a candidate for a diuretic. If a diuretic is given, there is a known statistical measure of its performance; it will work properly in a fraction of patients, that fraction perhaps dependent on the state variables, age, previous health history, etc. These complicated rules are contained in a number of subroutines appropriate to each function; the list includes subroutines for calculating urine output, leakage from the wound to the environment, passage throught the lymphatic system of edema fluid to the plasma volume (resorption of the edema), and the basic fluid administration (or therapeutic regimen). We propose to devote a substantial portion of this study to the development, calibration, verification and combination of these subroutines to form a model sensitive to therapeutic alternatives and representative of the best clinical judgements and histories available at the Peter Bent Brigham Hospital. As indicated above we propose to use the hematocrit properly to tune the model so that its parameters, in an unambiguous way, represent a "best fit".

For purposes of this exposition, Figure 2 shows some of the potential functions in symbolic or mathematical functional form only. The differential equations which define the volume changes per unit time can be solved simultaneously, subject to the constraint that the criterion function (for example, the mean-square-deviation between calculated and observed hematocrits) be minimized. This is a classical problem in control theory, and poses no major intellectual barriers. The simultaneous differential equations use the standard dot notation which indicates a rate of change or derivative with respect to time.

We have experimented with a very small sub-model abstracted from the complete model suggested in Figure 1. Our sub-model examines the interchange between plasma volume and the burn edema and is described in the following section.

Interchange Between Plasma Volume and Burn Edema

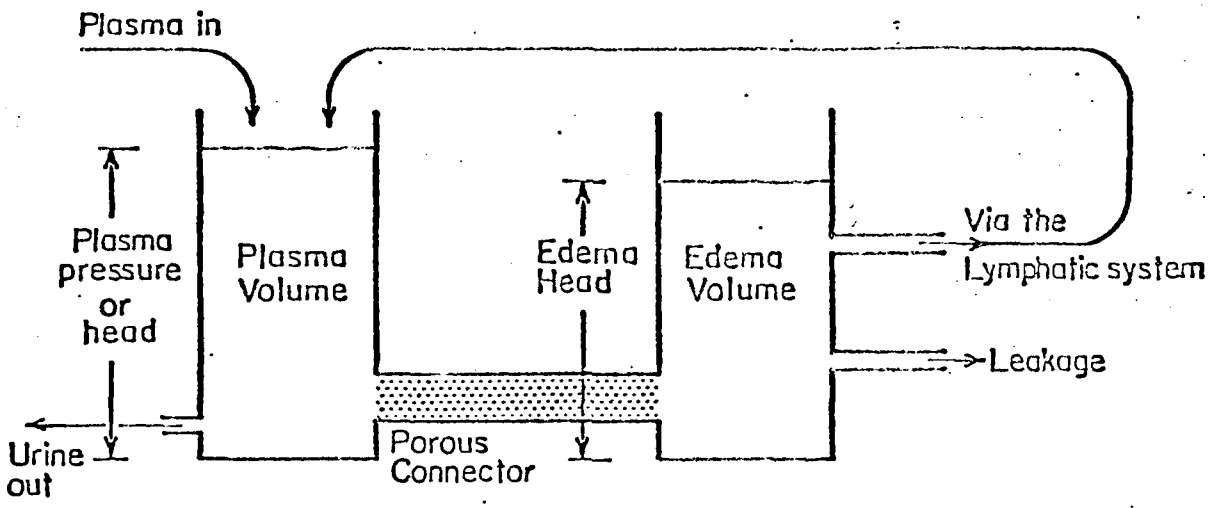
For purposes of presentation we have made some gross simplifications concerning the relationships between PV and burn edema and have coded some potential functions to indicate the calculations which would ultimately govern the entire model, Figure 1.

It would be very efficient if all of the functions were represented as analytic expressions so that the simultaneous solution of the estimation phase of the analysis (i.e. calculating the coefficients of the functions) might be handled analytically. But unfortunately the real world does not cooperate to that extent, and we find it necessary to solve the system in an iterative fashion, dividing time into increments small enough to maintain the validity of the calculation and large enough to yield meaningful solutions with reasonable expenditures of computer time. There is difficulty in establishing the "characteristic time interval" for simulations of this sort, the issue being one of compromising efforts to increase resolution while maintaining stability of the solution to the differential equations.

Figure 3 shows the sub-model, for which we established a hydraulic analogy which suggests that fluid is stored in two compartments connected by a porous medium. In the hydraulic analogy the fluids exert pressures proportional to the volumes in storage and inversely proportional to the base areas of the containers. That is, the pressures are given by the hydrostatic head or height of fluid (corrected for density) in each container. We assume here that the plasma and edema fluids are at the same density so that the hydrostatic heads alone are adequate to express the pressure differences transmitted across the connector tube.

Darcy's Law expresses the rate of flow through the porous tube: $q = kiA$, where q is the rate of fluid flow, i is the hydraulic gradient or difference in head divided by the length of the porous connector (so that i is dimensionless), A is the cross-sectional area of the tube and k is a constant of proportionality, commonly called the coefficient of permeability. As fluid moves from one compartment to the other, the volumes within the containers change so that the heads, and consequently the gradient i, change continuously with time, resulting in a continuously changing rate of transfer from one compartment to the other. This is a common problem in engineering, resulting from the filling and emptying of reservoirs in series, the use of town water tanks, etc. The analogous law in physiology is Starling's Law, which asserts that the rate of fluid transfer is proportional to the pressure gradient across a membrane (and some other arguments associated with the porosity of the membrane). [1,2,3,4,5,6,7]

In our sub-model, PV is augmented by the infusion of plasma and depleted by the outflow of urine. The burn edema loses fluid directly to the environment through evaporation and leakage, and through the lymphatic system by resorption of the edema fluid into the plasma volume. The purpose of this model is to develop time traces of the plasma volume and the burn edema, hoping thereby to show the effects on both of various rates of plasma administration, diuretics, percent and depth of burn, etc. It



Notes:

1. "Permeability" of Porous Connector changes over time.
2. Heads are calculated from Plasma and Edema volumes using "Area", an artifact for mapping accumulated volume into a pressure.

FIG. 3 SIMPLIFIED 2-COMPARTMENT QUALITATIVE MODEL

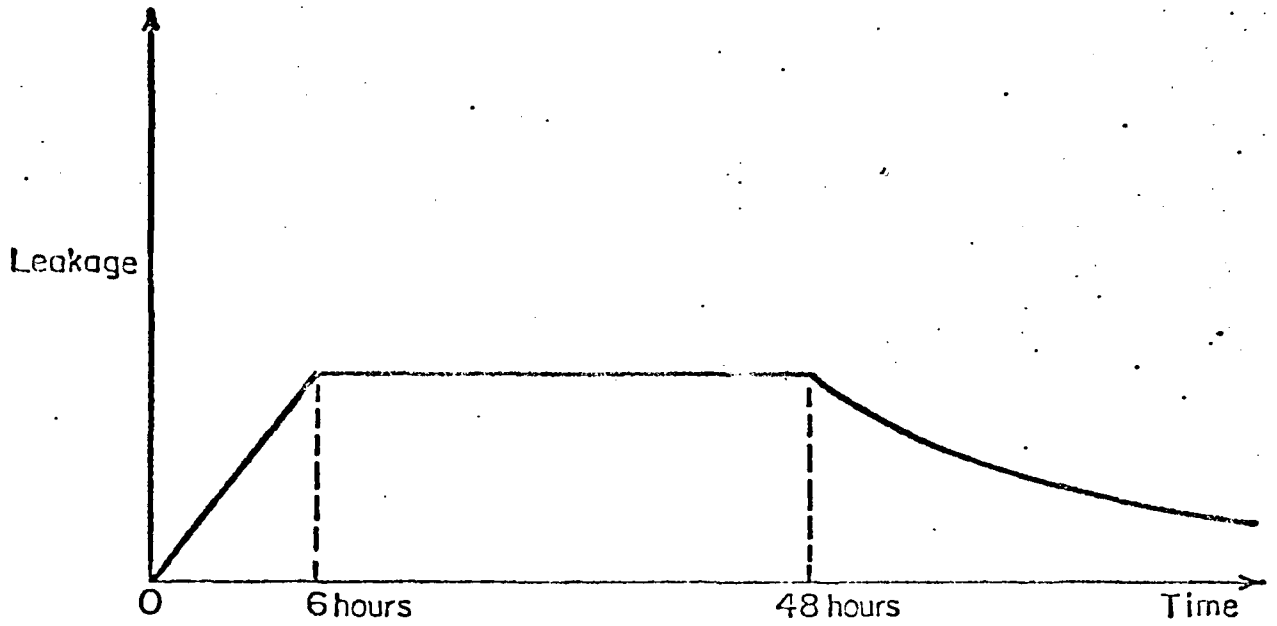
is hoped that by properly calibrating such a model so it provides a good descriptive fit to the hematocrit trace, we can then use the model as a prescriptive tool to study various treatment regimens. In other words, during its descriptive phase the model is "run backward" for calibration while in its prescriptive phase it is "run forward" to develop trajectories associated with a variety of alternatives and statistical variations within and among patients.

The sub-model has deterministic and stochastic components. We deal first with the deterministic functional forms and establish a few numerical results to show the qualitative nature of the interaction between the two compartments. It must be emphasized that no quantitative results are dependent on this demonstration; we present this sub-model to show the range of choice available to model makers when dealing with complex physiological problems, and to demonstrate how pieces of the problem can be individually attacked so that the entire system can be fabricated from its constituent parts. Following this, we will describe some of the stochastic (Monte Carlo) elements of the simulation, showing how within-patient and among-patient variations can be accommodated in this simple format.

The schematic diagram, Figure 3, contains enough information for purposes of following the calculation. The Main Routine expects initial values for the PV and edema volume, as well as the usual control variables associated with initiating the run. We also provide coefficients of the various functional forms; in the complete model, some of these coefficients may be the (intermediate) state-dependent outputs associated with other subroutines so that they are continuously updated. We ignore this complication in this simple sub-model.

The Main Routine first looks to Subroutine LEAK to estimate the leakage from the burn wound to the environment. Figure 4 shows the shape of the assumed function. Over the first few hours, here taken to be 6, the leakage increases linearly from zero to its maximal value, where it remains for 2 days. After 48 hours the leakage decreases exponentially, and in this trial run the coefficient is 0.9905 per hour so that in 24 hours the leakage is 80% (or 0.99524) of the leakage at the end of the previous day. After 2 days, the leakage rate decreases by 20% (of the current day's value) per day. The subroutine calculates the leakage appropriate for the current time interval (by calculating the average leakage throughout the interval and multiplying that average rate by the length of the interval).

Subroutine TREAT introduces plasma at a uniform rate throughout the interval. At this stage of model development the complications associated with a variable rate are not part of the program. The subroutine provides a plasma volume input



Note:

6 and 48 hours, the peak value, and the rate of exponential decay are program input variables, subject to change.

FIG. 4 LEAKAGE FROM BURN WOUND

equal to the plasma volume lost to the burn edema; that is, the loss in the previous time period is replaced by plasma inputs, although in its final form a much more sophisticated algorithm will be imposed.

Subroutine LYMPH deals with resorption of the burn edema, and therefore includes elaspsed time among its arguments. Studies show that lymph ducts are not open during the acute metabolic phase of the burn but that they open after a few days. In this didactic model, the early loss (per unit time) by resorption is always 10% of the excess edema volume, or volume in excess of the initial fluid stored in the edema compartment. After 48 hours the assumption is that the resorption doubles, whereupon the edema begins to shrink rapidly so that the actual resorptive flow becomes small in absolute volume.

Subroutine PRCENT modifies subsequent leakage calculations by adjusting the maximal leakage which can occur in the next time period, taking account of the patient's size, weight, sex, and percent burn.

Subroutine URIN calculates the total urine loss for the time period, taken here to be a constant unless a diuretic is added, whereupon the rate of urine production is doubled. A proposed method for modeling urine output is described below.

All these preliminaries having been performed, the routine is then prepared to balance the hydraulic forces exerted across the capillary membrane. This is performed in Subroutine HYD. The PV is incremented by the plasma and lymph inputs and decremented by the urine output, as suggested by Figure 3. The pressure exerted by the plasma is based on the average plasma volume during th time interval, divided by the "area" of the base of the plasma compartment. While the concept of the base area makes hydraulic sense, there is no physiological analog so the "area" is a theoretica construct which represents a mapping from plasma volume to oncotic pressure. It is convenient to call this mapping function the "area" by analogy to the hydraulic counterpart.

The edema volume is decremented by the leakage and loss to the lymphatic system, and the edema "area" is calculated. This area, as for the PV, is a mapping function but we give it the name "area". However, unlike the PV area, it is not constant but follows a time-dependent relationship which mimics the observation that edema fluid exerts its pressure across a membrane of non-constant extent. The functional form follows that of Figure 5. The left-hand portion is linear, the middle portion is constant and the right-hand portion follows an exponential decay. In this study the hourly exponential decay is taken to be 0.985 so that daily decay is at the rate of 0.70; that is within the right-hand portion of the curve the daily decay is 30% of the current area. The two times are 6 and 48 hours, as with leakage, and we assume that the intercept (at time zero) is 4 with a peak of 10. It bears repeating to note that these "areas" are not ordinary physical areas but scaling factors which represent the transmission of oncotic pressure and fluid flow between the burn edema and the plasma.

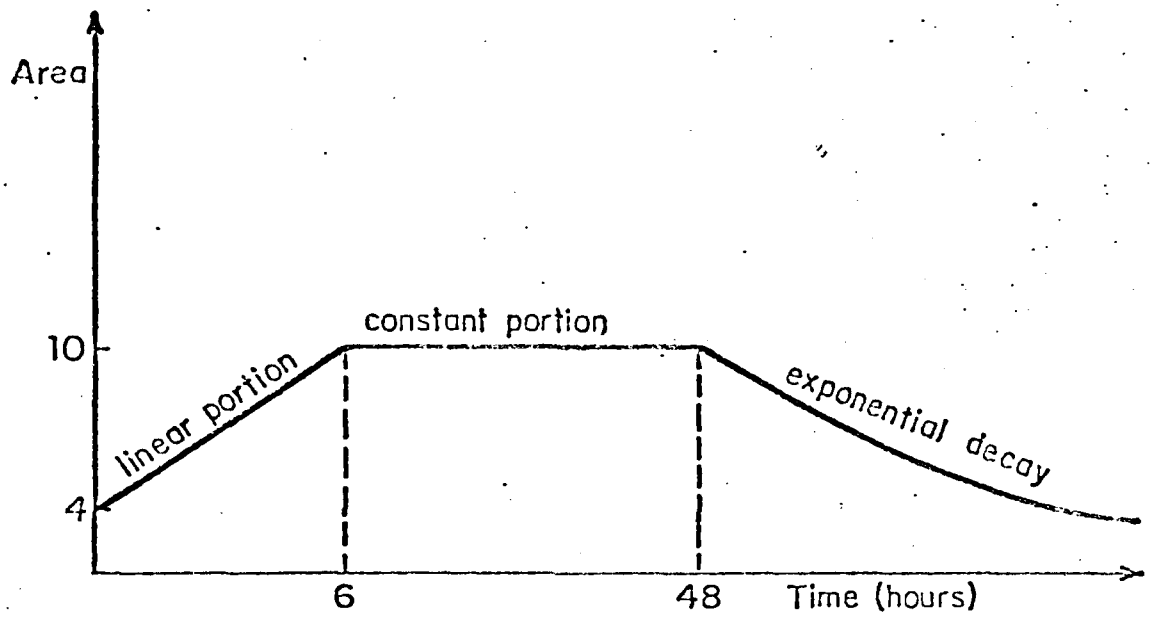


FIG. 5 "AREA" OF EDEMA COMPARTMENT AS A FUNCTION OF TIME

The area of the connecting link is assumed to vary over time and as a function of the pressure difference. This important assumption is required to allow the buildup of edema because under the hydraulic assumption the edema volume cannot increase while the pressure in that compartment exceeds that of the plasma compartment. When the system is in equilibrium the pressures are identical so there is no net transfer of fluid. When leakage occurs from the burn wound, fluid moves from the PV compartment to the edema but, if the hydraulic analogy holds exactly, the movement cannot continue beyond that time at which the pressures equalize, whereupon it becomes patently impossible for the edema volume to show further increase unless its "area" increases so that the edema pressure falls and allows further transfer of fluid from PV to the edema (Figure 3). That is the edema space is very compliant.[9] We do not know exactly the rate at which this area increase occurs, but we anticipate that it can be simulated numerically by the time dependent change in the area of the connecting link. This is accomplished in Subroutine AREA, whose arguments are the 2 fluid pressures and the elapsed time. For the test run we posit the use of a logistic function whose equation, is $20\,[1 + \exp(-0.8473(\text{pressure difference}))]^{-1} - 10$. This empirical fit mimics system behavior without explaining any of its physiologic characteristics, but in any event the fluid transfer is now readily calculated.

The PV is decremented by ΔV (the volume transferred from PV to edema) and the edema is incremented by the same ΔV. The calculations are now completed except for some minor bookkeeping and printing of intermediate output, whereupon the program considers another time interval (hour), 72 of which constitute a complete test run.

The program then considers another run of the same patient, all the results of which would be identical except for the inclusion of stochastic or random components. Each of the major subroutines described here includes a random component whose magnitude is proportional to the stanadard error of estimate associated with fitting empirical observations by the given functions. If the fit is particularly good the random component is small, and conversely. We have no reason to expect that the distribution of observations follows one standard density function or another, and much of our study will be directed toward identifying useful and appropriate functions. But here we incorporate normal densities merely to demonstrate inclusion of random errors in processes of this sort. Thus the standard error of estimate of each function is required as input data for the program. Normally distributed random numbers (zero mean, unit variance) are calculated by the program and used to perturb the deterministic formulations. No two runs will produce the same final output because of the influence of random factors, so that several runs from the same starting conditions can be made to show

not only the consequences associated with a particular trial protocol but the distribution of outcomes associated with each patient and each set of initial values. This represents the empirical fact that a group of patients, presumed identical in their clinical manifestations, will yield a distribution of results under the same therapeutic regimen.

After a group of runs is completed, and the results presented in convenient output format, the program systematically examines new patients, with new burn sizes, ages, heights, wieights, etc. The results of some of these computations are outlined below.

Results

This section describes results of preliminary experiment using the sub-model. The relationships between plasma volume (PV) and edema formation are exercised over a range of parameters to determine the general shape of the curve which represents edema formation and resorption. It must be empahsized that this discussion is not definitive and refers at this time only to the qualitative aspects of model behavior. The purpose of studying this small excised portion is to show that clinically reasonable arrays of data can be generated by carefully tuning the parameters of a model which includes causal descriptions and statistical curve-fitting components.

Nine teen "patients" or case studies were run including a baseline case and eighteen subsequent cases in which the parameters of the hydraulic analogue were systematically varied to generate a range of typical responses (measured in terms of edema formation). The model, apart from whatever physiologic and conceptual errors exist in the functions, is incomplete in that the compartment for PV is not connected to any other components of the system except that for edema, and thus depends entirely on fluid administration (inputs) to maintain appropriate volume levels. The computer program for this segment of the model performs the calculations in the following order: (i) leakage from the burn wound is calculated as a function of the burn size and the time since the burn;[10,11,12,13,14] (ii) urine output is calculated as a constant with a random perturbation, modified if a diuretic is administered; (iii) resorption of the edema is calculated as a function of edema volume and time since the burn (which together define the capacity of the lymphatic system to remove fluid from the edema and place it into the PV); (iv) having thus established the volumes in the PV and edema compartments, the oncotic pressures are estimated and the net fluid transferred from the PV to the edema is estimated; (v) externally administered fluids are provided in accordance with an algorithm which replaces the outflow from the PV; (vi) output summaries are printed and the program cycles through another iteration or time period.

Each of the four functions (leakage, urine output, resorption and fluid transfer) contains a random component proportional to the standard deviation of that constituent of the flow regimen. In this preliminary version of the model the standard deviations (provided among the input data) are constants although in subsequent versions of the model it might be more appropriate to let the standard deviation depend on some of the system state variables. We made three runs of each case using different sequences $(0,1^2)$ random normal deviates in each, to test the sensitivity of edema formation to modest random perturbations in the values computed for the presumed functional forms.

Figure 6 gives the shape of a typical time trace of edema formation and resorption. The edema compartment is assumed initially to have a volume of 100 units, which increases rapidly by a factor of 3-6 with the peak usually occurring within the first six times units (hours, quarters of days, days or whatever) and then falling precipitously within another 6 time units to a volume approximating the initial volume. The edema volume then gradually increases again, reaching a second and lower peak at 48 time units, whereupon it trails off gradually throughout the remainder of the trial period (144 units).

Not every combination of parameters of the several transfer functions generates an edema of the shape shown in Figure 6. Some combinations lead to steadily expanding edema, with no apparent feedback or control on edema size, while others fail to develop the early peak and near-exponential decay characteristic of clinical observations. These are manifestations of local instability of the solution to the governing differential equations. While we do not demonstrate that the clinical situation can be represented by the hydraulic analog suggested here, and do not prove that the hydraulic analog is characterized by logistic functions of the sort described here, and do not prove that the parameters of that logistic function are known without error, we demonstrate at least that certain combinations of parameters make sense while others do not, and that these combinations can be further tested for robustness by split sample techniques and jackknifing. Moreover, if the results so indicate, the model can be applied to animal studies for verification outside the range of observations available at this time. This proposed hierarchial analysis, moving from postulated model to calibration with split samples and ultimately to evaluation outside the limits of observation is part of our strategy for developing new therapeutic criteria potentially different from those now in use.

Numerical Values

Returning to the numerical results, we systematically varied the standard deviations of the several transfer functions, the time or phase constant of the porous area function, the use of diuretics and the maximal value attained by the area function.

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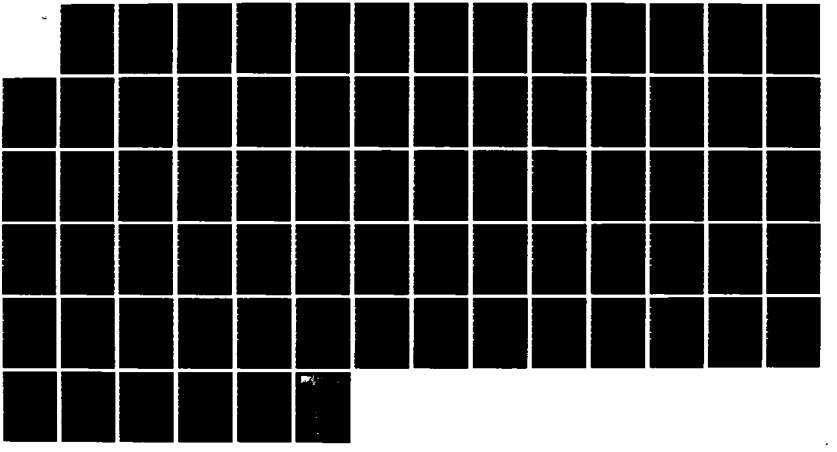
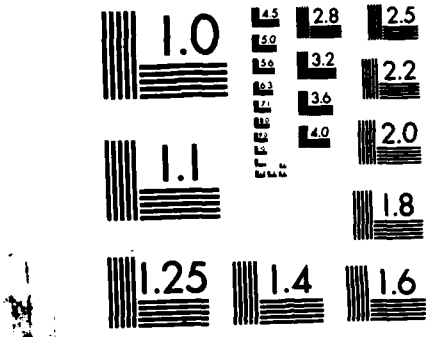




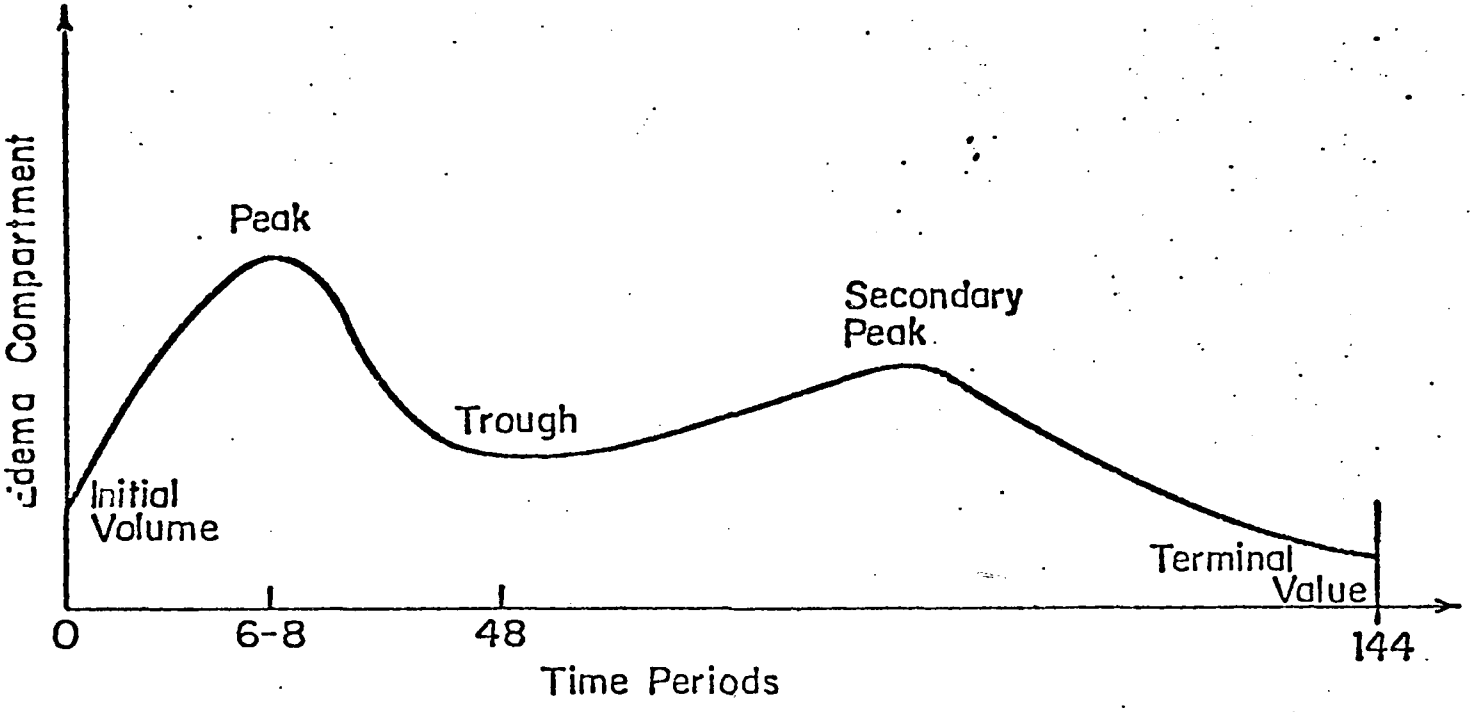


FIG. 6 EDEMA FORMATION

Of course, even dividing these into a coarse grid, the problem is enormous because the number of feasible combinations far exceeds our capacity systematically to simulate results. Selective sampling in the multi-dimension sample space was required, and for purposes of this proposal we found that eighteen perturbations demonstrated a range of behavior which will enable us ultimately to fine-tune the model (and its parameters) to develop a reliable predictive model for testing various therapeutic regimens.

The criterion for goodness-of-fit of our tuning procedure could be multi-dimensional or scalar; for ease of computation, and because data are readily available from the hospital charts; we have chosen a scalar criterion: minimize the sum of squares of deviations between projected and observed hematocrit levels. Selection of a scalar precludes the necessity of weighing the various components in arriving at a criterion of fit. This is particularly useful because the several indices might not be uniformly available, thus leading to discrepancies in assessing their relative importance and their relative precision. It will be recalled from the schematic diagrams of the entire model (Figures 1 and 2) that the hematocrit level is readily calculated from the state variable values associated with red blood cell volume and PV, so the criterion function is easily evaluated.

Assignments of parameter values are not unique because many different combinations of parameters could yield the same residual variation (as measured by the squared deviation between estimated and observed values of the hematocrit). Clearly a better fit could be obtained by increasing the number of parameters in the model; if this were to continue unchecked there would be so many parameters that all the observations would be fit exactly by a polynomial of suitably high degree. But for interpolating between estimated values, or for extrapolating beyond the observations, such a polynomial would represent an unwise fitting procedure; we are precluded from such a model by analysis of variance and significance applied at each stage of the analysis.

The 18 cases plus the base line study produced 9 combinations for which there was no stable edema formation and no convergence to an asymptote. No convergence was obtained for a time phase or lag less than 10 units, or for an areal peak less than 10 units. All other variable combinations in this small sample produced convergence, and in these 10 cases the properties of the edema formulation are measured by two statistics; the ratio of the greatest (initial) peak to the secondary peak (at approximately 48 time units) and the ratio of the greatest peak to the final volume in the edema compartment at 144 time units. For most values of the standard deviations, these ratios are remarkably consistent for all three runs which comprise a single patient or study; for particularly large values of the standard deviations, the ratios and edema volumes show larger fluctuations attributable to sample (within-patient) error.

Not much physiology or strategy can be learned from these numerical results; we merely gain confidence in our ability more closely to model physiologic performance under complex sets of fluid fluxes. Because this model is didactic in that it is abstracted from a much larger, connected system, there can be no meaningful interpretation laid to the deduced model behavior except to note in passing that it is not inconsistent with observed clinical experience abstracted from patient records.

Urine Output Sub-Model

This proposal emphasizes the role of a stochastic simulation model to identify and evaluate new therapeutic regimens in burn care. Consequently it generates conflict between those who utilize mathematical models only when there is some known, direct causal connection between inputs and outputs and those who fit statistical models when no causal link can be identified. We propose a strategy which effects a compromise between these two approaches.

It is useful to focus on one more component of the fluid balance model during the course of the project, similar analysis will be done on the other components. Consider the estimation of urine output (UO) for a given time period. Clearly the simulation of any regimen for fluid balance must include a module for estimation of urine output because of its role in representing renal function. The causal model approach would lead to a symbolic or numerical representation of the essential renal functions which govern the production and elimination of urine. All the important hormones, clearance rates, secretory rates, etc. would be required, along with detailed knowledge of the physiology of renal function -- how all these hormones and functions are related -- and the mathematical formalisms which represent the essence of these relationships. Is the physiology significantly different in a burned patient? If so, how do the extent, location and time of the injury modify renal function? What are the implications of other disease and prior treatment?

Identification of mathematical functions to satisfy all these questions by recourse to first principles represents a hopeless task; detailed examination of the literature and inquiry of those on the forefront of research in this area give little cause for optimism.

The statistical or "black box" approach is numerically appealing but intellectually unsatisfying. It lies at the opposite extreme in that it requires no understanding of renal physiology, no insights into specification of controlling or important variables; its only requirement is a data base to be manipulated by a computer. The process is very simple -- urine outputs are tabulated as the dependent variable, along with all the independent variables which might govern urine production and which are already available from existing records or easily measured. This data array is then subject to conventional multiple linear regression, whereby the best least-squares estimate of UO is given as a linear combination of the arguments or independent variables. Modifications of the conventional formulation are available, so that variables can be added in the order of their importance (stepwise regression), a variety of transformations on the dependent and independent variables can be made, various conditions on accepting elements in the analysis can be imposed, etc. But none of these deals with the fundamental problem of using even a good regression equation as a predictor in those cases for which independent variables lie outside the range of the data base. In other words, the regression equation is merely a result of curve fitting under a well-defined criterion, and it might be wholly inappropriate to utilize the derived function as a predictor for therapeutic combinations which have not been experienced

in the data base and which therefore might educe significantly different responses. The use of a causal model which reverts to first principles is intellectually more appealing because the inviolate laws apply over a wider range of independent variables.

A compromise methodology is suggested -- one which uses physiologic insights and large data bases but which does not place us entirely at the mercy of the numerical curve-fitting procedures. We propose to use multivariate statistical techniques, particularly factor analysis and canonical correlation analysis, to suggest phenomenologically justifiable combinations of independent variables. The technique requires the prior specifications of some form of model, typically linear; it posits the combination of variables into clusters which accord with good sense. For example, we argue that urine output is a function of free water clearance, osmotic load and filtration rate and renal blood flow and plasma oncotic pressure. In addition, there may be further dependence on the state of the patient as measured by his age, percent and location of burn, disease history, current and recent history of urine output, etc. Many of these factors cannot be measured directly but can be estimated through a combination of easily available surrogates... The set of equations on the following page is illustrative and suggestive; it does not purport to provide definitive estimates of the essential physiological factors and their combinations, but rather a set of parameters which might usefully be employed in screening existing records, animal experiments and ultimately human patients.[15,16,17,18,19]

The values F_i are called factor values; there are attached to each of these additional indices j and t to identify the patient and the time. The coefficients f_{ik} represent a contribution of the kth variable to the ith factor, and the two subscripts on the measurements represent the contribution of the jth patient at time t. The problem of factor analysis is to estimate all the coefficients f_{ik}, to calculate the factor scores F_{ijt} and then ultimately to calculate the coefficients a_i which estimate urine output at a time (t+1) as a function of combinations of laboratory and clinical values which are aggregated or clumped into numerical surrogates of physiological components of the complete system. Standard computer programs are available to perform these calculations for large numbers of observations and large numbers of patients.

The purpose of the exercise is to generate a set of factor scores such as those which might be used to fill Table II.

$$F_{0j} = f_{01}(\text{Age})_j + f_{02}(\%\ \text{Burn})_j + f_{03}(\text{History})_j + f_{04}(\text{Liver Failure})_j + f_{05}(\text{Body Weight})_j + \cdots$$

$$F_{1jt} = f_{11}(\text{Age})_{jt} + f_{12}(\text{Fluid in})_{jt} + f_{13}(\text{Edema})_{jt} + f_{14}\ (\text{Diuretic})_{jt} + \cdots$$

$$F_{2jt} = f_{21}(\text{BUN})_{jt} + f_{22}(\text{Na})_{jt} + f_{23}(\text{Sugar})_{jt} + f_{24}(\text{Mannitol})_{jt} + f_{25}(\text{K})_{jt} + f_{26}(\text{Na intake})_{jt} + \cdots$$

$$F_{3jt} = f_{31}(\text{Hct})_{jt} + f_{32}(\text{BP})_{jt} + f_{33}(\text{CVP})_{jt} + f_{34}(\text{CO})_{jt} + f_{35}(\text{Peep})_{jt} + \cdots$$

$$F_{4jt} = f_{41}(\text{TP})_{jt} + f_{42}(\text{Alb})_{jt} + \cdots$$

$$F_{ijt} = \sum_{k=1}^{m} f_{ik}\ (\text{Variate})_{jt}$$

$$\text{U.O.}(t+1) = a_0 F_0 + a_1 F_1 + a_2 F_2 + a_3 F_3 + a_4 F_4$$

for some patient j at time t.

TABLE II.

Patient	Time	U.O.(t+1)	U.O.(t)	F_0	F_1 (free water)	F_2 (osmotic load)	F_3 (renal flow)	F_4 (oncotic pressure)
1	1			F_{01}	F_{111}	F_{211}	F_{311}	F_{411}
	2				F_{112}	F_{212}	F_{312}	F_{412}
	.							
	.							
	.							
	n				F_{11n}	F_{21n}	F_{31n}	F_{41n}
2	1			F_{02}	F_{121}	F_{221}	F_{321}	F_{421}
	2				F_{122}	F_{222}	F_{322}	F_{422}
	.							
	.							
	.							
	n				F_{12n}	F_{22n}	F_{32n}	F_{42n}
...								
P	1			F_{0p}	F_{1p1}	F_{2p1}	F_{3p1}	F_{4p1}
	.							
	.							
	.							
	n				F_{1pn}	F_{2pn}	F_{3pn}	F_{4pn}

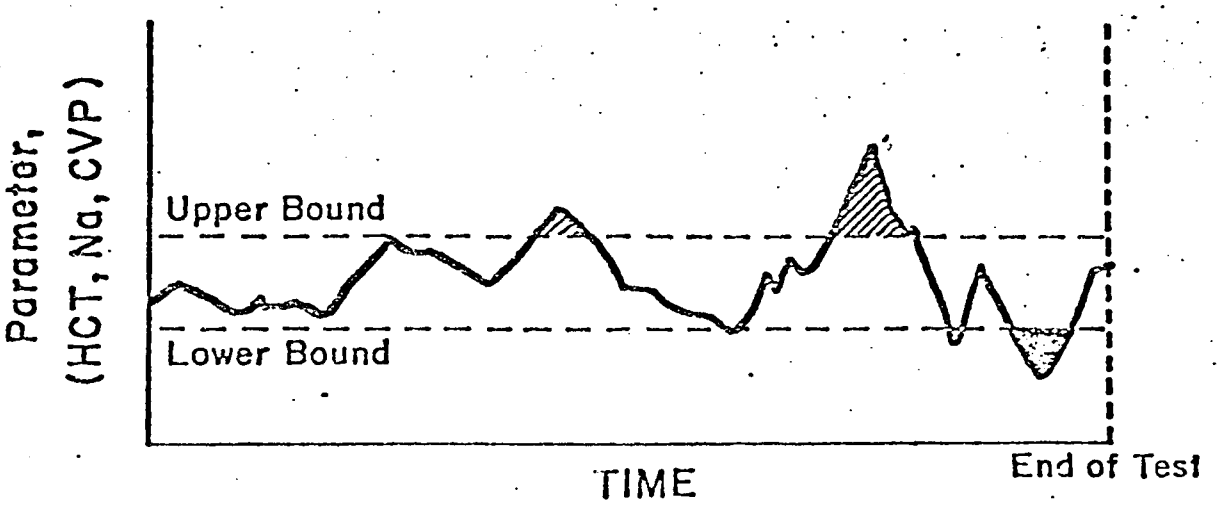
When one or another of these estimators of urine output is utilized in the fluid balance model, assuming that an appropriate number of iterations are run to exercise the statistical properties of the estimating function, the parameter z_1 (urine output in the figure) can accurately be represented and included in the model, leading ultimately to an assessment of the therapeutic regimen.

Ultimately it will become necessary to reconcile differences between the control-theoretic or statistical model and the causal or physiologic model. The reason for this requirement is obvious; the control model must make good sense if it is to be accepted and used by the medical profession. It must not violate well-established empirical fact. This is not to say that it cannot overturn traditional therapeutic regimens, but if it is to do so it must closely reproduce those important observations from which there can be no argument. If it violates good sense, the model will not be accepted. Another important reason to insist on close convergence of the 2 model forms is that the causal model can be used as a training aid by simulating expected and deviant patient response. Alternative strategies can be projected, clinical errors can be evaluated in terms of their consequences, and new research can be directed in terms of the importance of refining existing theories; all of these can be accomplished by computer simulation without risk to patients. The first therapeutic regimen to be tested on the model will be the current algorithm. The performance of these therapeutic strategies or regimens will be evaluated by a series of 'indices of performance'.

The values in the table are then subject to conventional regression analysis using a least-squares criterion or some similar formalism, from which the coefficients a_i are derived and used to validate prior judgments about the causal connnections because the factor scores are orthogonal so that F_i-values are statistically independent variables, whereupon the regression coefficients a_i represent changes in dependent variable (UO) associated with unit changes in factor scores. This is a significant departure from the usual regression format, in which the coefficients are not phenomenologically appropriate because correlation might obtain among the so-called independent variables. In other words, conventional regression coefficients do not represent expected changes in the dependent variable associated with unit changes in the independent variables because at least in expectation, changing an independent variable x_i implies changing all the other variables x_j with which x_i is correlated. The BIMED series is available at our computing installation to perform factor analysis.

Canonical correlation is related to factor analysis, but differs in the fact that system output is not limited to a single variable but is itself a linear combination of output variables. Suppose patient response is measured by several numerical indices $y_1, y_2,\ldots,y_n$, and that the various control variables or medical decisions are identified as $x_1, x_2,\ldots,x_m$. In traditional regression analysis or in factor analysis it is appropriate to write $y_1 = y_1(x_1,x_2,\ldots,x_m)$, $y_2 = y_2(x_1,x_2m\ldots,x_m)$, etc. In other words, each of the output variables is some function of the inputs or decisions, and least-squares analysis finds that set of coefficients which, for a prescribed fitting function, maximizes the correlation or minimizes the sum of squares of residuals. Canonical analysis asks a slightly different question: Is there a linear combination of outputs, say $a_1y_1 + a_2y_2 + a_ny_n$, which is maximally correlated with some other linear combination of decisions, say $b_1x_1 + b_2x_2 + \ldots + b_mx_m$? Essentially, can two vectors (a) and (b) be found so that the scalars produced by calculating the dot or inner product associated with each "observation" on the vectors (y) and (x) are maximally correlated. We seek from canonical analysis some measure of how the set of variables which defines patient performance is aggregated and correlated against that set of variables which defines therpeutic regimen.

Another class of analysis is defined by probit and logit techniques in which the "output" or system performance is divided into four groups with similar performance (for example, UO < 25 mℓ /hour, 25 ≤ UO < 50, 50 ≤ UO < 100, etc) whereupon, for any combination of "state" and therapeutic or decision variables, the analysis gives the probability of having the output lie in any one of the several disjoint or non-overlapping output states. Thus a probability density on urine output can be developed, with which we can utilize appropriately distributed random numbers to simulate statistically valid estimates of urine production as a function of the relevant phenomenological or causative agents.



Time Trace of Patient Response-
Calculation of Indices

FIG. 7

Indices of Performance

A series of indices has been developed to measure the quality of fluid therapy. These indices are to be applied by a separate computer algorithm. Currently the indices are used to evaluate the quality of fluid therapy in burn patients managed in the Burn Unit at the Peter Bent Brigham Hospital. A trial is underway in the Burn Unit comparing conventional fluid therapy of burn patients administered by physicians to conventional fluid therapy administered to the patients by a compnter algorithm. A significant portion of this research would be directed at defining indices which measure the effectiveness of various fluid therapy strategies, the nature of the patient response to these strategies, and the "smoothness" of the trajectory or course in the first few days following burn injury. For purposes of discussion and to indicate that this is a viable strategy, we offer a few indices for which the results have been calculated from a recent series of patients whose therapy was directed by physicians compared to a very small group of three patients whose therapy was directed by the existing computer algorithm.

Our indices measure deparatures from accepted ranges of parameters which are surrogates for the quality of fluid therapy. At this time we have not assigned any weighting factors to the several values because the assessment of such factors is part of the proposed research effort. The purpose of this discussion is to demonstrate that reasonable indices can be deduced from patient records, calculated unambiguously in accordance with a computerized algorithm, and arrayed against outcome in such a way as sensibly to reflect the course of recovery.

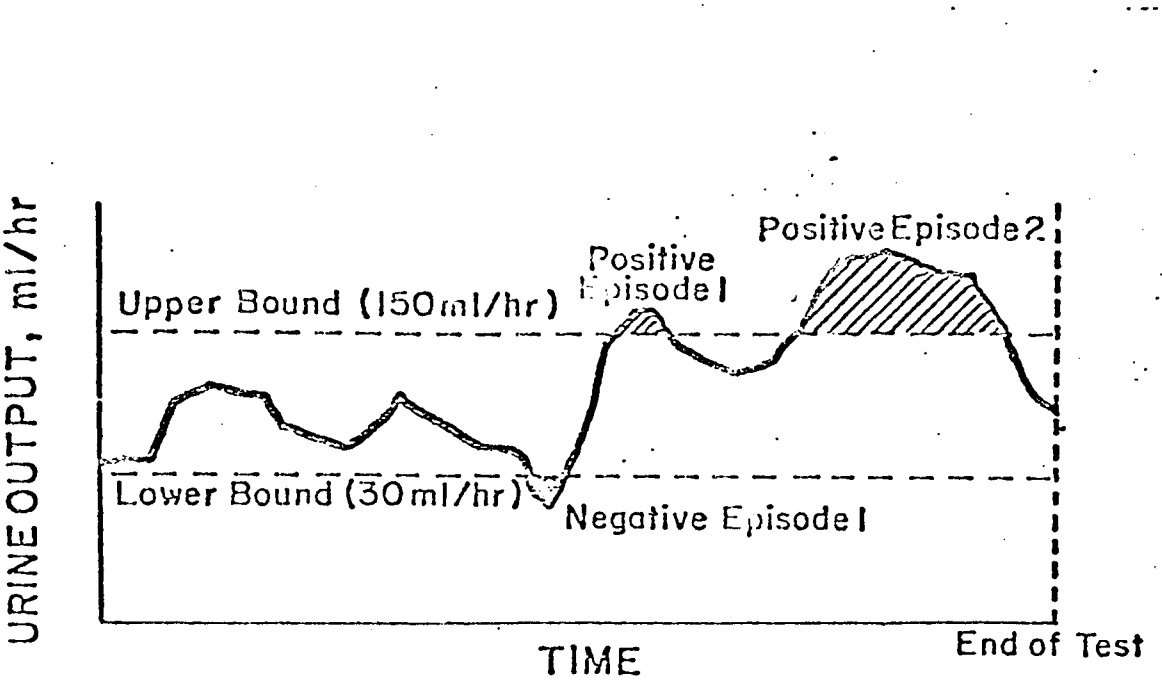
Index values are based on recorded sequences of hematocrit, serum sodium, central venous pressure, urine output, and body weight. Consider Figure 7 which shows a time trace of a parameter (hematocrit, serum sodium or CVP); a continuous function is shown, although in practice discrete points would be available. Clinical judgement prescribes acceptable upper and lower bounds on the parameter; these reflect the range within which it is considered acceptable for the parameter to vary. For hematocrit, the bounds are 38 and 44; for serum sodium they are 137 and 144; and for CVP they are 0 and 8. With reference to the figure, the cross-hatched area is the area above the upper bound and the solid area is the area below the lower bound of the parameter in question, and the index measures these areas. However, in order to

render the index dimensionless so that the absolute length of record does not materially affect the index itself, the areas outside the boundaries must be normalized to yield a dimensionless scalar parameter. We propose that the areas outside the range be divided by the rectangular area between the upper and lower boundaries so that the ratio (not necessarily less than unity) represents a scalar measure of performance.

There might be clinical evidence to suggest that oscillations above the boundary are more (or less) significant than oscillations below; subsequent research might verify such judgement but at the moment our computer program calculates one index for positive perturbations, one for negative perturbations and one for total perturbations (in either direction). Further research might also suggest that the boundaries change with time in that an acceptable course would accommodate wide swings early in the treatment but that these swings should stabalize as therapy progresses, and that the "penalty" for failing to attain stability could be reflected by increasing the stringency of the requirements by narrowing the range of allowable variation.

Thus for each of the three parameters--hematocrit, serum sodium and CVP--three indices are computed for each patient. These indices are based on the time sequence of observations, with a linear function interpolated between subsequent readings. In some cases data are missing from the records; any number of reasons might account for this. The program linearly interpolates the missing records and then proceeds in the usual manner. The resulting indices are called: Hct+, Hct-, Hct, Na+, Na-, Na, CVP+, CVP- and CVP.

An index of urine outputs is based on the cumulative departure from stated boundaries. Consider Figure 8 which shows a time trace of urine output. Excursion above an hourly output of 150 ml is called a positive episode and each excursion below 30 ml/hour is called a negative episode. The figure shows two positive episodes of different duration and one brief negative episode (perhaps treated vigorously by diuretics). The cross-hatched area represents the cumulative output excess, and the area divided by the number of positive episodes is the average urine excess given there is a positive episode. Similarly, the solid area below the lower boundary represents the urine deficit and the total deficit divided by the number of negative episodes represents the average urine deficit given there is a deficit. Linear interpolation to reconstruct missing data is not clearly indicated because in some instances the reported urine outputs represent cumulative values over more than one time period. Thus a missing value might imply simply that the next recorded value should be spread over more than one interval; the program performs this operation if the data are flagged appropriately. In the absence of such a flag, the program assumes that the next available datum is not cumulative so it interpolates linearly between observed values. The index is divided into three components: UO+, which represents the average urine excess per positive episode; UO-, which represents the



Time Trace of Urine Output -
Calculation of UO+, UO- and UO

FIG. 8

average urine deficit per negative episode; and UO, which represents the total urine volume outside the acceptable range divided by the total number of positive and negative episodes.

The next index of performance is a gross measure which defines the amount of edema formation. The calculation is based on the percentage gain in body weight, expressed in terms of the pre-burn weight, divided by the percent burn. There are thus 14 indices in all, but 12 of them are divided into four groups of three, with each group representing a positive departure, a negative departure and a total departure from clinically acceptable ranges.

The results of the pilot study are shown in Table III. Note that the total departures for the hematocrit, sodium and CVP are greater for the original or control group than for, thre three cases managed by the computer. The percent of weight gain is also greater without the computer, but the urine deviations are smaller. This last can be explained by the fact that most of that difference is on the UO+ index while the UO- index, indicating the onset of renal failure, is much higher for the control group. It could be argued that the three computer-managed cases are especially selected, but in fact they are simply the last three burns to enter the Bartlett Unit and contain one 90 percent burn; this represents a higher fraction of severe burns than in the control group.

During the course of this research effort additional statistical properties of the indices can be determined to evaluate the quality of fluid therapy and the nature of the trajectory or course. A variety of multivariate techniques (factor analysis, canonical correlations, cluster analysis, etc.) involving the correlation structure among the individual indices and their linear combinations, will be attempted using standard multivariate packages available at our computer installation.

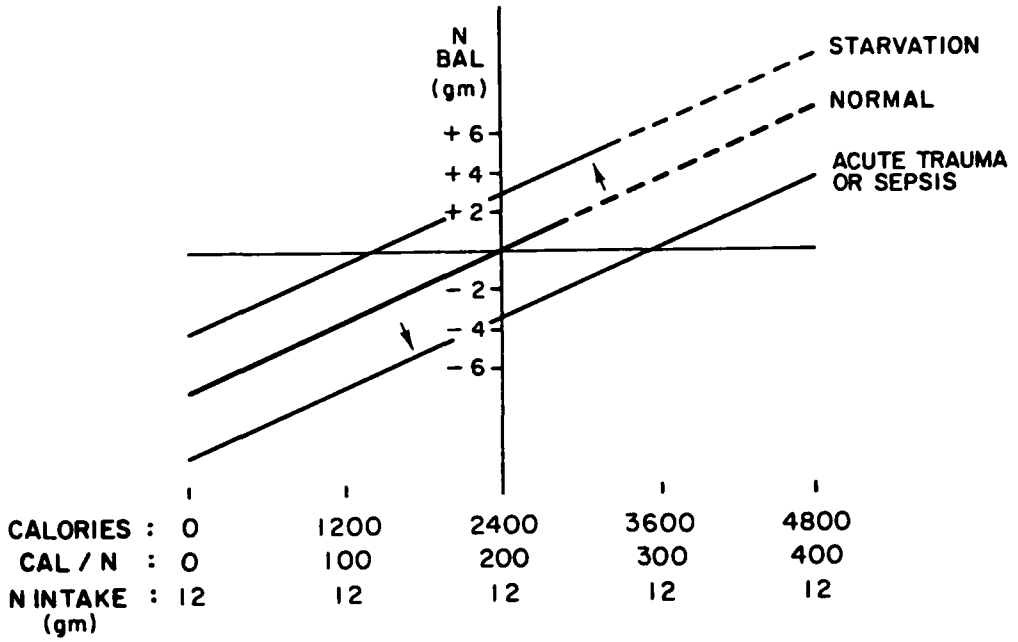
These indices of performance will be used to evaluate the performance of the fluid model when different fluid therapies are applied to the model. For example, if a fluid therapy strategy is designated to try and minimize the amount of edema that accumulates after burn injury, this new strategy will be tested on the burn model and its performance will be evaluated by the indices.

TABLE III

RESULTS OF PILOT STUDY

	3 Cases		24 Cases	
	Computer		No Computer	
Index	Mean	Standard Deviation	Mean	Standard Deviation
Hct+	.081	.075	.194	.321
Hct-	.291	.355	.206	.312
Hct	.372	.426	0.400	.368
Na+	.032	.054	.037	.079
Na-	.058	.070	.167	.221
Na	.090	.051	.203	.216
CVP+	0.000	.010	.04	.08
CVP-	0.00	.0	.0	.0
CVP	0.00	.010	.04	.08
UO+	5632	9211	3149	6530
UO-	8.67	8.08	40.8	156.8
UO	5607	9233	3040	6549
Gain/%Burn	.153	.124	.213	.192

EFFECT OF CALORIES ON NITROGEN BALANCE
NITROGEN CONSTANT – CALORIES VARIED

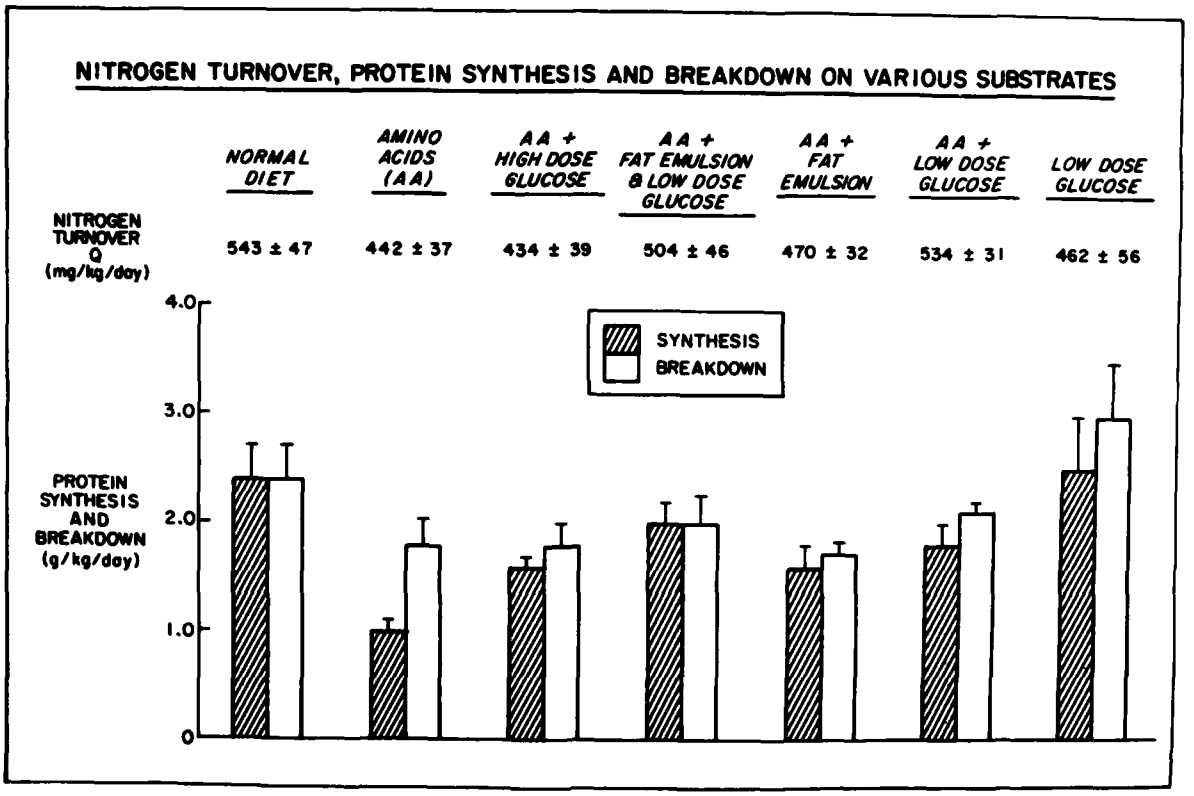


This chart shows nitrogen balance (vertical axis) plotted against calorie/nitrogen ratio (horizontal axis). Nitrogen intake is assumed constant at an adult norm of 12 grams per day. Calorie nitrogen ratio varies as the ratio of non-protein calories to nitrogen in the intake. It ranges from zero at the extreme left, to 400 at the extreme right.

The center line shows the calorie/nitrogen slope in a normal fasting individual receiving nutrient only by vein. Where no calories are provided (an example would be the infusion of amino acids alone) nitrogen balance is strongly negative. The line crosses zero (i.e., the normal zero balance) at a calorie/nitrogen ratio of 200. This postulates an intake of 2,400 calories, about the adult daily normal, with the nitrogen intake of 12 grams. The point at which the line crosses zero is called the "calorie/nitrogen mandate for equilibrium." In the normal it is approximately 200. Although slight positive balances can transiently be produced in the normal, the line does not progress upwards very far and is thereafter dotted because strongly positive balances are not achieved in the normally nourished.

Starvation without stress (i.e, starvation without fever or trauma) moves the calorie/nitrogen slope to the left. This is shown in the left hand line. Here amino acids without carbohydrates are used somewhat more efficiently than in the normal. The body appears to be "[illegible]" for protein synthesis and achieves it at lower calorie/nitrogen ratio. The ca[illegible]nitrogen mandate for zero balance is lower than in the normal long periods of ti[illegible]il the body cell mass is back to normal. Stated otherwise, the achievement [illegible] is "facilitated" in the unstressed starving state.

Severe stress ([illegible] fever, infection) move the calorie/nitrogen slope to the right (right hand line). Here much more severe losses of nitrogen are noted as low calorie/nitrogen ratios. The calorie/nitrogen mandate for zero balance is moved upwards to 350-400 (i.e., 3,600-4,800 calories with 12 grams of nitrogen). Stated otherwise, the achievement of protein anabolism is made more difficult by severe stress, much higher levels of intake of non-protein energy being required to achieve net protein synthesis.



Above are shown whole body protein turnover data (Q), synthesis and breakdown, for a variety of intravenous substrate mixtures studied in normal (fasting) human volunteer subjects. The 3 columns to the left (oral diet, amino acids alone, and amino acids with high dose glucose) demonstrate a reduction in Q when shifting to intravenous diet, and a clear increase in synthesis rate with added glucose. The four columns to the right (substrate mixtures as shown above each column) confirm the effect of added energy sources on synthesis rates; the column to the extreme right (low dose glucose alone) suggests an increased protein turnover rate on subcaloric carbohydrate without nitrogen.

THE EFFECT OF HORMONE AND SUBSTRATE INFUSION ON GLUCOSE DYNAMICS IN MAN USING (2-^{3}H) GLUCOSE AS THE TRACER

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ABSTRACT

Minimum glucose mass, glucose replacement rate, and glucose space were measured using ($2-^3H$) glucose as the tracer.

Seven healthy male subjects were separated into two groups of six patients each, five subjects being used in both studies. Group I underwent Glucagon, Norepinephrine and Glucagon + Norepinephrine infusion, and Group II underwent hydrocortisone and insulin infusion.

The results showed that when the subjects were rendered hyperglycaemic by glucagon, norepinephrine, and hydrocortisone infusion, minimum glucose mass and glucose turnover increased, glucose space was unaffected. During insulin infusion glucose concentration fell significantly ($p=0.001$), minimum glucose mass fell to a lower degree and the glucose replacement rate increased. There was an increase in the glucose space after insulin infusion suggesting that part of the fall in glucose concentration was due to redistribution of the glucose over a larger space.

The changes achieved in glucose concentration after hormone infusion was shown to be the result of a complex combination of alteration in minimum glucose mass, replacement rate and space.

Subsequently, five normal male volunteers (Group III) were subjected to infusions of Dextrose at a ratio of 0.578 mmol/min and 2.89 mmol/min and also of a 3.4% solution of amino acids (Freamine II^R). After a period of 22 hours infusion of each of these substrates, a dose of ($2-^3H$) glucose was given intravenously and from the decay curve, minimum glucose mass, glucose replacement rate and glucose space were calculated.

During amino acid infusion and low dose glucose infusion, neither glucose mass, glucose replac ement rate or glucose space were significantly altered but during a high dose glucose infusion, minimum glucose mass was elevated ($p=0.007$), glucose replacement rate was elevated ($p=0.16$) and glucose space was elevated similarly, ($p=0.16$) and glucose space was elevated similarly, ($p=0.01$).

It was observed that there was no summation effect of glucose output by the liver and the glucose infusion rate, suggesting that, in the circumstances studies, hepatic glucose output was reduced in proportion to the rate of exogenous glucose infusion.

INTRODUCTION

The introduction of isotopically labelled glucose enabled studies of the dynamics of glucose metabolism to be undertaken. Using a single injection of Carbon-14 glucose, Baker et al[1] and Shreeve et al [21] estimated the size of the exchangeable glucose mass and glucose replacement rate. Hormonal control of glucose metabolism has been investigated on the basis of changes in serum concentration of glucose and hyperglycaemia and hypoglycaemic hormones for many years. The introduction of isotopically labelled glucose has allowed closer study of the changes in glucose dynamics to be made.

De Bodo et al [4] reported a comprehensive animal study in which he demonstrated the effects of glucagon, norepinephrine and insulin upon glucose removal and replacement rates, showing increases in glucose turnover in both hypo- and hyperglycaemic states induced by insulin and glucagon respectively. The close relationship between the action of glucagon and catecholamines and glucocorticoids has been domonstrated by Kuschke et al [13] and Le Febvre et al [14], both in relation to their hyperglycaemic and cardio-vascular effects.

The importance of glucagon and catecholamines together with adrenocortical steroids in the response to acute injury and chronic catabolic illness has received much attention both in man and animals. However, the effect of these hormones upon glucose dynamics in normal man has not been clarified. Similarly, insulin has been used in man to reverse or neutralise the effects of raised levels of these hormones caused by either exogenous administration, or endogenous release associated with injury or disease. However, precise details about the action of any of these hormones upon glucose dynamics in man remain scarce.

Continuous infusion of glucose and amino acids separately or in combination have been used extensively in the management of nutritionally depleted and injured patients.[3,4] Detailed studies have been reported of the effects of glucose infusion upon nitrogen concentration in normal volunteers.[19,23] Long et al [15] have taken these investigations further using Carbon-14 glucose to detect changes in glucose replacement rates during glucose infusion.

Blackburn et al [3] described the use of an isotonic amino acid solution for maintaining nutrition in subjects requiring parenteral feeding. If one assumes that the carbon chain accompanying the nitrogen molecules was oxidised via the carbohydrate route to provide energy, then it is possible that the contribution of these carbon skeletons may be detected as modifying the endogenous glucose replacement rate.

This communication reports a study of the effect of infusion of glucagon, norepinephrine, hydrocortisone, insulin and glucose and amino acids upon minimum glucose mass, glucose replacement rate and glucose space in man. A single injection of (2-^{3}H) glucose was used as the tracer.

MATERIALS AND METHODS

Three groups of patients were studied; seven healthy male volunteers, having given informed consent, were divided into two groups of six subjects each.

Group I underwent a control study and were then subjected to a series of intravenous infusions of: (a) Glucagon^R(Lilly) 0.53 µg/kg/hr, (b) L-Norepinephrine (Levophed^{R}Winthrop) 0.077 µg/kg/hr, and (c) Glucagon 0.53 µg/kg/hr + Norepinephrine 0.077 ug/kg/hr. Each subject was fasted for 12 hours before each study and then, apart from the control study, were infused for three hours. At the beginning of the control study and subsequently after the first hour of the infusions, 500 µCi of D - (2-^{3}H)

glucose (Amersham/Searle) in 30 ml normal saline, was given by rapid intravenous injection, and blood samples taken at intervals for estimation of serum glucose, insulin, plasma glucagon and serum glucose specific activity and tritiated water. The specific activity of the glucose was 56 mCi/mg and by paper chromatography the preparation had a radiochemical purity of 98%.

Subjects in Group II (which differed from Group I by only one subject) underwent a control study and were then infused with: (a) Soluble Insulin (Lilly) 0.75 units/kg/hr, and (b) Hydrocortisone Sodium Succinate (Solu-Fortef^{R}-Upjohn) 0.75 mg/kg/hr, each for three hours. During the control study and after the first hour of the infusions, 250 uCi of (2-^{3}H) glucose was injected rapidly intravenously in 30 ml normal saline. As in Group I, all subjects were fasted for 12 hours before the study and then blood samples were taken at intervals for the estimation of the same parameters as in Group I, with the addition of serum cortisol estimations.

In Group III, five normal human volunteers, having given informed consent, were fasted for 12 hours and then given an intravenous injection of 250 uCi D-(2-^{3}H) glucose (Amersham/Searle) in 30 ml normal saline. Blood samples were taken at intervals over the subsequent two hours for estimation of serum glucose, insulin, growth hormone and plasma glucagon, together with serum glucose specific activity.

After a further 12 hours fast, the subjects were given an intravenous infusion of a 3.4% solution of amino acids (Free Amine^{R}II) delivered throughout 24 hours at a constant rate by an infusion pump (IM&D Corp), prepared as described by Tweedle et al.[10] A total volume of three litres was given containing 30.8 g amino acid/1 with 4.5 g nitrogen/1 giving a total of 92.4 g amino acids (13.5 g Nitrogen each day. After 22 hours of infusion, 250 uCi (2-^{3}H) glucose was given and blood samples collected

as described above.

Following the amino acid infusion, an infusion of 5% glucose was given over 24 hours, the subject receiving three litres containing 833 m mol (150 g) glucose at a rate of 0.578 m mol/min (104 mg/min). After 22 hours, 250 uCi of (2-^{3}H) glucose was given and blood sampled as before.

Finally, an infusion of 25% glucose was given so that over the 24 hour infusion period three litres of water containing 4166 m mol (750 g) of glucose at a rate of 2.89 m mol/min (521 mg/min). After a further 22 hours, a further dose of 250 uCi (2-^{3}H) glucose was given.

The subjects were all permitted distilled water by mouth ad libitum.

ANALYTICAL METHODS

Serum glucose was measured using a glucose oxidase method (Sigma) [2], serum immunoreactive insulin and growth hormone concentration were estimated using a combined double antibody radioimmunossay [11], glucagon was measured by a radioimmunoassay using a 30K antibody [6], and serum cortisol was estimated using the method of Nelson and Samuels [18].

Estimation of (2-^{3}H) glucose specific activity

Estimation of (2-^{3}H) glucose specific radioactivity was based on separation of (2-^{3}H) glucose counts from tritiated water by evaporating all water to constant weight dryness from a deproteinised sample of serum at a temperature of 37°C. The method was checked by adding known quantities of tritiated water and tritiated glucose to serum samples. The percentage removal of the tritiated water by evaporation and the percentage recovery of (2-^{3}H) glucose were measured. Using a series of 10 replicate standards tritiated water removal as 98 $\pm$ 5% (S.D.) and tritiated glucose recovery as 99 $\pm$ 6% (S.D.). Specific activities of (2-^{3}H) glucose and tritiated water determined in duplicate on each serum sample taken and mean values were used in calculation.

CALCULATION

The serum glucose concentrations in each subject were constant throughout each run within 5% (S.D.). Steady state kinetics could therefore be applied, and the glucose replacement rate could be calculated by the standard equation (Gurpide, Mann and Liebermann, 1963) [8]; Heath and Barton, 1973 [9]:

(1) $$\frac{D}{\int_0^{\infty} s\,dt} \text{ mmol/min}$$

and the minimum glucose mass by the equation (Katz, Rostami and Dunn, 1974) [12]:

(2) $$\frac{D \times \int_0^{\infty} ts\,dt}{\left(\int_0^{\infty} s\,dt\right)^2} \text{ mmol}$$

Volume of distribution of glucose was calculated by the equation:

(3) $$\frac{\text{Minimum glucose mass (mmol)}}{\text{Serum glucose concentration (mmol/l)}} \text{ l}$$

For experiments lasting four hours the s-t integral in equations (1) and (2) were calculated in two ways: 1. Using all the date to 240 minutes by the method of Heath and Cunningham (1975) [8]; 2. Using the data only to 120 minutes, the above method was modified (Heath, D.F., personal communication) by obtaining the last mean squares line of best fit to the logarithms of the last three points. From the line were calculated the value of the slopes and the best estimate of the point at the first of the three times, which was used in the calculation of the area in place of the experimental point. Otherwise the calculation was as before.

The ts-t integral in equation (2) was calculated as follows: (Heath, D.F., personal communication). In the calculations of the s-t integral the s-t

curve was split into segments each represented by a specific single exponential function. From each function the ts-t integral was obtained by analytical integration over the same time interval, and the integrals were summed.

At 120 minutes the total amount of tritiated water present was calculated and compared with the number of tritium counts which had been injected as (2-^{3}H) glucose. This provided an estimate of the transfer of tritium from glucose to tritiated water expressed as a percentage. The residual (2-^{3}H) glucose counts were similarly expressed as a percentage of the administered dose enabling an estimate of the total percentage recovery of all administered tritium counts to be made.

RESULTS

The results of these studies are expressed as the mean $\pm$ 1 standard deviation and differences compared using students t-test for paired data.

GROUP I (Tables I - IV)

(a) Glucagon Infusion

Serum glucose levels during the glucagon infusion were 6.20 $\pm$ 1.12 mmol/l, higher ($p=0.05$) than those occurring in the control study which were 4.68 $\pm$ 0.46 mmol/l. Minimum glucose mass was 1.660 $\pm$ 0.499 mmol/kg compared with control values 1.161 $\pm$ 0.378 mmol/kg. Glucose replacement rate was 0.01433 $\pm$ 0.00255 mmol/kg/min, compared with control values of 0.00867 $\pm$ 0.00128 mmol/kg/min ($p=0.001$) and the glucose space was 265.8 $\pm$ 37.38 ml/kg with control values of 247.5 $\pm$ 61.29 ml/kg. Serum insulin levels (Table VI) were increased during glucagon infusion to 12.70 $\pm$ 4.55 μU/ml, but this was not highly significant when compared with control values of 6.8 $\pm$ 2.85 μU/ml. Serum growth hormone levels were marginally depressed during glucagon infusion, compared with control values.

Plasma glucagon was markedly elevated to 908 ± 304 pg/ml compared with control values of 60 ± 40 pg/ml (p=0.001).

(b) Norepinephrine Infusion

Serum glucose was elevated to 5.02 ± 0.27 mmol/l, minimum glucose mass was slightly decreased to 1.140 ± 0.101 mmol/kg and glucose replacement rate was slightly raised to 0.01172 ± 0.00183 mmol/kg/min (p=0.006). The glucose space was 227.6 ± 21.8 ml/kg which was lower than the control levels. Serum insulin levels were not significantly higher than the control level at 9.50 ± 2.88 μU/ml. Serum growth hormone levels were depressed to 1.40 ± 0.90 ng/ml, and plasma glucagon levels (Table IV) were within the normal range at 52 ± 25 pg/ml.

(c) Norepinephrine + Glucagon Infusion

Serum glucose was significantly elevated at 5.87 ± 0.40 mmol/l (p=0.005). Minimum glucose mass was elevated at 1.843 ± 0.841 mmol/kg, and glucose replacement rate was increased to 0.01272 ± 0.00294 mmol/kg/min (p=0.002). The glucose space was 263.0 ± 40.7 ml/kg, higher than control values. Serum insulin levels were significantly elevated at 22.50 ± 9.69 μU/ml (p=0.02) and serum growth hormone levels were within the normal range. There was a marked elevation in plasma glucagon levels at 8,545 pg/ml with a wide scatter.

During the Norepinephrine infusion in Group I (b) and (c), blood pressure was continuously monitored and a consistent rise in diastolic and systolic blood pressure occurred during the infusion with a mean rise of 10 mm Hg.

GROUP II (Tables VI - XII)

(a) Hydrocortisone Infusion

Serum glucose concentration was raised to 5.40 ± 0.42 mmol/l compared with a control value of 4.85 ± 0.19 mmol/l (p=0.05). Minimum glucose mass increased to 1.324 ± 0.220 mmol/kg, compared with a control

of 1.074 ± 0.110 mmol/kg (p=0.05), glucose replacement rate was 0.01472 ± 0.00239 mmol/kg/min with a control of 0.01278 ± 0.00122 mmol/kg/min, and the glucose space was 245.5 ± 42.9 ml/kg, which was not significantly different from the control value of 221.3 ± 20.4 ml/kg. Serum insulin levels were within normal range at 9.00 ± 3.69 μU/ml with a control of 9.83 ± 4.62 μU/ml. The serum growth hormone and plasma glucagon levels of both control and infusion studies were within the normal range. Serum cortisol levels were 46.78 ± 13.41 μg/ml in the infusion group compared with 9.15 ± 3.64 μg/ml in the control series.

(b) Insulin infusion

Serum glucose concentrations were significantly lowered at 2.47 ± 0.49 mmol/l (p=0.0001). The minimum glucose mass at 0.785 ± 0.147 mmol/kg was lower than control values (p=0.02). The glucose replacement rate was 0.01728 ± 0.00483 mmol/kg/min (p=0.06), which was the highest in any group in these studies. Glucose space increased to 333.9 ± 111.0 ml/kg (p=0.06). Serum insulin was raised by the infusion to 76.5 ± 21.8 μU/ml and serum growth hormone was significantly increased at 21.3 ± 8.3 μg/ml. Plasma glucagon also showed an increase to 204 ± 57 pg/ml (p=0.01) and plasma cortisol was insignificantly different from control values.

When the results of these calculations based on a 5–120 minute curve were compared with the results based on a 5–240 minute curve, no significant differences were found in either the control groups or the groups undergoing hormone infusion, suggesting that the glucose specific activity decay curve was a straight line between 120 and 240 minutes.

During the control studies, the amount of tritium detectable as tritiated water at 120 minutes was 73 ± 14.4 % of the total tritium counts given (assuming that ^{3}H–O–H as evenly distributed throughout the

total body water), and analysis of the remaining counts as ($2-^3H$) glucose and those converted to tritiated water revealed that there was a 102.0 ± 12.0 % recovery of all administered tritium.

GROUP III (Tables XIII - XVIII)

(a) Amino Acid Infusion

Mean serum glucose concentration after 22 hours of amino acid infusion was 4.54 ± 0.21 m mol/l compared with control values of 4.85 ± 0.21 m mol/l, the difference being insignificant. Glucose mass was 1.265 ± 0.250 m mol/kg compared with a control of 1.076 ± 0.123 m mol/kg.

Glucose replacement rate was 0.01117 ± 0.00172 m mol/kg/min with control value of 0.01294 ± 0.00128 m mol/kg/min. The glucose space also, at 276.0 ± 54.1 ml/kg, was insignificantly different from control levels at 221.5 ± 22.8 ml/kg. Serum insulin levels (6.2 ± 2.38 μU/ml) were within the control range (9.8 ± 5.2 μU/ml) and both amino acid infusion and control growth hormone levels were normal. Plasma glucagon levels were elevated at 163 ± 98 pg/ml compared with control values of 65 ± 20 pg/ml. Plasma cortisol levels were unaffected by the infusion.

(b) 5% Glucose Infusion

Serum glucose concentrations were raised at 5.90 ± 0.65 m mol/l ($p=0.03$) and minimum glucose mass increased to 1.473 ± 0.323 although this increase was not highly significant. Glucose replacement rate at 0.01311 ± 0.00200 m mol/kg/min; amd glucose space (250.1 ± 36.6 ml/kg), were both in the same range as control values. Serum insulin concentrations were elevated to 13.6 ± 7.9, although this was not significant. Growth hormone, glucagon and cortisol levels were within the normal range.

(c) 25% Glucose Infusion

During the 25% glucose infusion, serum glucose concentration increased to 6.77 ± 1.19 m mol (p=0.04), and was associated with a rise in minimum glucose mass to 2.467 ± 0.641 m mol/kg (p=0.007). The glucose replacement rate increased to 0.04202 ± 0.01555 m mol/kg/min (p=0.016) with an expansion of the glucose space to 359.1 ± 67.9 ml/kg (p=0.01).

Serum insulin concentration was increased compared with control levels to 37.2 ± 20.8 μU/ml (p=0.03), serum growth hormone and cortisol levels were unchanged, but plasma glucagon levels tended to be lowered to 23 ± 15 pg/ml.

DISCUSSION

Glucose Turnover Methods

The use of (2-^{3}H) glucose in this study allowed minimum glucose mass, glucose replacement rate and the glucose space to be calculated easily and with a minimum of disturbance to the subject.

When our control results are pooled and compared with values recorded in the literature [15,20,21,22] (Table XIX), where ^{14}C-glucose has been used as the tracer, it was found that the ^{14}C-glucose studies gave mean minimum glucose mass values about 30% higher at 1.448 ± 0.432 mmol/kg. There were, however, similar estimates of the glucose space. The association of a higher mass in the presence of the same glucose space may in part be due to an increased glucose concentration in the subjects in the ^{14}C-glucose studies.

It was anticipated that the use of (2-^{3}H) glucose as a tracer might yield lower values for minimum glucose mass and higher values for glucose replacement rate than if ^{14}C-glucose were used, on the basis of

recirculation of ^{14}C label into new glucose, or futile cycling of (2-^{3}H) glucose.

However, although the series are not strictly comparable, there was a marked difference between the mean values for minimum glucose mass comparing the two labels, the scatter of results reducing the level of statistical significance. Comparison of the glucose replacement rates using the two labels shows that there was no significant difference between the estimates using (2-^{3}H) glucose and results using ^{14}C-glucose labels published in the literature. It is particularly encouraging to note that the glucose replacement rates in our human subjects using (2-^{3}H) glucose were close to the direct estimates of hepatic glucose output by Myers in 1950[17] and Gump et al in 1974[7], in their studies in a similar group of human volunteers. This would indicate that although the effects of recycling and futile cycling were not excluded, any errors they might cause are fairly small in human subjects.

Hormone Infusion

The interplay between hormones which raise or lower the serum glucose concentration, has long been recognised as a crucial factor in the control of glucose haemostasis. In this study, there was elevation of the serum glucose concentration in response to infusions of glucagon with and without additional norepinephrine and also during a hydrocortisone infusion. The hyperglycaemia was more pronounced during the glucagon infusion, and glucagon with norepinephrine infusion. In contrast there was significant hypoglycaemia during the insulin infusion, the serum glucose concentration being halved.

In the dynamic steady state which existed after the initial period of equilibration during these infusion studies, the serum glucose concentration remained stable at its new level, implying that glucose

replacement was equal to glucose removal. However, under the influence of glucagon and norepinephrine alone and together, there was a significant increase in the glucose replacement rate. De Bodo et al [4] have demonstrated in animal studies that glucagon infusion is associated with an initial fall in glucose removal together with a rise in glucose replacement rate resulting in a net rise in serum glucose concentration. The system then stabilised at this new level, but with a maintained increase in glucose replacement and removal, and a similar pattern occurred under the influence of catecholamines. It was clear that we were seeing the same process in our human volunteers, with the increase in glucose replacement associated with the hyperglycaemia being a manifestation of the dynamic steady state establishing itself at a higher serum glucose concentration, under the influence of the hormones.

During insulin infusion it was noted that there was an increase in glucose replacement rate associated with the hypoglycaemia, once again this was in agreement with the data of De Bodo et al [4] in which they demonstrated the converse reaction to that which occurred during glucagon infusion. In response to insulin there was an inhibition of glucose replacement with an increase in glucose uptake until a new dynamic steady state was reached at a lower serum glucose concentration, when the glucose replacement rate increased to the new higher level equilibrating with glucose uptake. Hydrocortisone infusion had no significant effect on glucose replacement rate.

During the infusion of hormones which caused an increase in blood glucose, it was noted that the hyperglycaemia was associated with a proportionately greater increase in minimum glucose mass. This would tend to suggest an underlying increase in glucose space maintaining

glucose concentration at the lower level. During glucagon infusion, concentration increased by 32% and mass by 44% with an increase in glucose space of 7%. During glucagon and norepinephrine infusion, concentration increased by 25%, mass by 59%, but with an increase in glucose space of only 6%. Hydrocortisone infusion caused an increase in glucose concentration by 11%, mass by 23%, and space by 11%. In contrast, norepinephrine, while causing an increase in concentration of 7%, was associated with a fall in mass of 2%. As might be predicted theoretically, glucose space diminished to compensate for this fall in mass. Insulin infusion was associated with a 51% fall in glucose concentration but only a 27% fall in mass. Glucose space increased by 51%.

It is not possible to explain all these discrepancies simply on the basis of changes in the minimum glucose mass distributed uniformly within the changing glucose space. Glucose is distributed throughout the extra-cellular water, and Morgan et al [16] have shown that glucose occurs at very low concentrations within cells. This intra-cellular glucose must be considered as part of the total exchangeable glucose. As it is clear that the minimum glucose mass is not distributed evenly about its space, it is clear that increases in the amount of glucose within the cells can cause an increase in the minimum glucose mass without altering the size of the glucose space. During glucagon and norepinephrine infusion, it is probable that the portion of the discrepancy between the increases in glucose concentration and mass might be explained by an increase in the amount of glucose within the intra-cellular part of the glucose space. During hydrocortisone infusion, changes in glucose concentration within cells is likely to be occurring to a lesser extent as more of the discrepancy can be

explained by the change in glucose space. During insulin infusion, glucose concentration falls by the same amount as glucose space increase, but the percentage fall in glucose mass is half that occurring in glucose concentration. This can only mean that a significant proportion of the glucose mass is intra-cellular and that the fall in glucose concentration after insulin infusion must be explained, at least in part, by glucose redistribution rather than utilisation.

It is well known [16] that a prime action of insulin in stimulating glucose metabolism is to enhance the transport of glucose across sensitive cell membranes, increasing glucose metabolism within the cell by means of increased substrate availability. It is thus not surprising that the fall in serum glucose concentration is to a degree caused by redistribution across a larger space and it is not necessarily a result of increased glucose utilisation.

It may be seen from the two groups of control data that there is a difference in the glucose replacement rate with the two different doses of label. In the light of the foregoing data and discussion, it is quite possible that the discrepancy could be explained by the different mean serum insulin levels in the two groups, but the amount of glucose given as label was so small as to be highly unlikely to alter glucose concentration or cause an insulin response.

This study shows that the changes in serum glucose concentration after hormone infusion are the result of a complex combination of alterations in minimum glucose mass, replacement rate, and space, and in particular suggests that changes in glucose concentration occur to carying extents within different compartments of the glucose space as a result of the actions of the various hormones upon glucose transport and utilisation.

Substrate Infusion

The groups of subjects in this study were similar to those described by Tweedle et al [23], undergoing amino acid infusion, and Wolf et al [24], undergoing amino acid, high dose glucose and low dose glucose infusion. During amino acid infusion there was no significant change recorded in serum glucose, insulin or growth hormone concentrations. However, there was a rise in plasma glucagon levels which was reflected in a minimum glucose mass and a glucose replacement rate which were within the normal range and inevitably accompanied by an unchanged glucose space.

Tweedle et al [23] observed that if the energy yield of the infused amino acids is calculated on the basis of all the carbon skeletons being metabolised via the carbohydrate pathway then 400 calories might be expected from this source, which if considered in terms of glucose, means an equivalent of 555.5 m mol (100 g) per day or 0.385 m mol/min. This is much lower than the measured glucose replacement rate of 0.01117 m mol/kg/min (0.855 m mol/min). However, it is clear that in this model where there exists a dynamic steady state with glucose replacement being equal to glucose removal, glucose replacement rate remained within normal limits. This implies that the hepatic output of glucose from gluconeogenesis could have been supplied to the extent of 0.385 m mol/min of glucose by carbon skeleton from the administered amino acids instead of being supplied from endogenous sources.

During the infusion of 5% glucose giving a dose of 833 m mol daily, it was noted that the serum glucose rose to 5.90 m mol/l. This was accompanied by a small, though non significant, rise in insulin concentration and a normal glucagon level which is consistent with the results obtained by O'Connell et al [19]. It was notable that in this

group also there were no significant changes in minimum glucose mass, glucose replacement rate, and glucose space compared with the control studies. However, glucose infusion at this rate 0.578 m mol/min is still lower than the measured glucose replacement rate in our subjects of 0.01311 m mol/kg/min (1.005 m mol/min).

The lack of any significant difference between the control glucose replacement rate and that during 5% glucose infusion implies that glucose replacement from endogenous sources was diminished to an amount approximately equivalent to the rate of glucose infusion as suggested in a similar study by Long et al [15]. It is possible that the small increase in insulin concentration was enough to suppress glucose mobilisation.

During 25% glucose infusion, there was a much larger increase in serum glucose concentration which differed from the results obtained by O'Connell et al [19], but was similar to the data of Wolfe et al [24], however, we did encounter the same rise in serum insulin concentration. Associated with the rise in serum glucose there was a highly significant increase in both minimum glucose mass and glucose replacement rate. The rate of infusion of exogenous glucose was 2.89 m mol/min which was rather less than the measured glucose replacement rate of 0.04205 $\pm$ 0.01555 m mol/kg/min (3.222 m mol/min).

Associated with this there was an increased glucose space. It is interesting to note the association between the combination of increases in glucose replacement rate in excess of the infusion rate and increased serum insulin concentration.

In conclusion, it would appear that glucose infusion will increase glucose concentration with an associated rise in glucose mass but unless an infusion of a 6-carbon substrate from glucose, or carbon skeletons from amino acids, exceeds the resting glucose

replacement rate, then no significant changes occur in glucose space replacement rates. This implies a fall in glucose output by the liver equivalent to the rate of infusion.

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TABLE I

GLUCOSE TURNOVER STUDY –
GLUCAGON + NOREPINEPHRINE INFUSION

Control Study

Name	Yrs Age	Ins Height	Kg Weight	m^2 Surface Area
A.C.	37	72	74.2	1.94
W.W.	28	76	79.6	2.10
D.T.	25	73	83.5	2.08
C.L.	22	71	83.5	2.04
P.Mc.	32	71	71.4	1.91
W.P.	38	74	76.0	2.0
$\bar{x}$	30.3	72.8	78.0	2.01
SD	6.47	1.94	5.0	0.08
SE	2.64	0.79	2.0	0.03

TABLE II

GLUCAGON AND NOREPINEPHRINE INFUSION

SERUM GLUCOSE CONCENTRATION m mol/l

Subject	Control	Glucagon	Norepinephrine	Glucagon + Norepinephrine
A.C.	4.22	5.61	4.89	5.67
W.W.	5.44	5.39	4.94	6.28
D.T.	4.61	5.83	5.11	5.61
C.L.	4.22	8.39	5.50	6.44
P.Mc.	4.94	5.61	4.72	5.44
W.P.	4.66	6.39	4.94	5.78
$\bar{x}$	4.68	6.20	5.02	5.87
SD	0.46	1.12	0.27	0.40
SE	0.19	0.46	0.11	0.16
Diff. from Control P =		0.05	insig	0.005

TABLE III

GLUCAGON AND NOREPINEPHRINE INFUSION

	MINIMUM GLUCOSE MASS m mol/Kg			
Subject	Control	Glucagon	Norepinephrine	Glucagon + Norepinephrine
A.C.	0.845	1.493	1.186	1.657
W.W.	1.555	1.468	1.196	1.196
D.T.	0.837	1.148	1.025	1.311
C.L.	1.133	2.594	1.239	3.482
P.Mc.	1.689	1.502	1.004	1.181
W.P.	1.108	1.808	1.191	1.892
$\bar{x}$	1.161	1.669	1.140	1.843
SD	0.378	0.499	0.101	0.841
SE	0.154	0.204	0.041	0.343
Diff. from Control P =		insig	insig	insig

TABLE IV

GLUCAGON AND NOREPINEPHRINE INFUSION

Subject	GLUCOSE REPLACEMENT RATE m mol/Kg/min			
	Control	Glucagon	Norepinephrine	Glucagon + Norepinephrine
A.C.	0.00972	0.01678	0.01539	0.01411
W.W.	0.00777	0.01561	0.01094	0.01550
D.T.	0.00739	0.00944	0.01028	0.01205
C.L.	0.00755	0.01394	0.01117	0.00717
P.Mc.	0.00922	0.01550	0.01150	0.01367
W.P.	0.01044	0.01467	0.01105	0.01400
$\bar{x}$	0.00867	0.01433	0.01172	0.01272
SD	0.00128	0.00255	0.00183	0.00294
SE	0.00052	0.00105	0.00072	0.00116
Diff.from Control P =		0.001	0.006	0.002

TABLE V

GLUCAGON AND NOREPINEPHRINE INFUSION

Subject	GLUCOSE SPACE ml/Kg Control	Glucagon	Norepinephrine	Glucagon + Norepinephrine
A.C.	200.3	266.1	242.6	291.5
W.W.	285.6	272.4	242.0	244.9
D.T.	181.4	196.8	200.5	233.7
C.L.	208.9	309.2	225.3	263.4
P.Mc.	341.6	267.6	103.1	216.9
W.P.	267.3	283.0	252.2	327.5
$\bar{x}$	247.5	265.8	227.6	263.0
SD	61.29	37.38	21.80	40.70
SE	25.02	15.26	8.90	16.62
Diff. from Control P =		insig	insig	insig

TABLE VI

GLUCAGON AND NOREPINEPHRINE INFUSION

HORMONE LEVELS

	Insulin μu/ml	Glucagon pg/ml	H.G.H. ng/ml
Control	6.83 ± 2.85	60.0 ± 40.1	5.03 ± 6.02
Glucagon Infusion	12.70 ± 4.55	980 ± 304	3.18 ± 3.33
Norepinephrine Infusion	9.50 ± 2.88	52 ± 25	1.40 ± 0.90
Glucagon + Norepinephrine Infusion	22.50 ± 9.69	8454 ± 1306	2.43 ± 2.09

TABLE VII

GLUCOSE TURNOVER STUDY –
INSULIN AND CORTISOL INFUSION

Control Study

Name	Yrs Age	Ins Height	Kg Weight	m^2 Surface Area
A.C.	37	72	74.2	1.94
W.W.	28	76	79.6	2.10
D.T.	25	73	83.5	2.08
C.L.	22	71	83.5	2.04
W.P.	38	74	76.0	2.00
W.M.	34	72	70.0	1.91
$\bar{x}$	30.7	73	77.8	2.01
SD	6.62	1.79	5.39	0.08
SE	2.70	0.73	2.20	0.03

TABLE VIII

INSULIN AND HYDROCORTISONE INFUSION

SERUM GLUCOSE CONCENTRATION m mol/l

Subject	Control	Insulin	Hydrocortisone
A.C.	4.78	1.94	5.00
W.W.	4.83	2.72	5.28
D.T.	5.11	2.67	5.05
C.L.	4.83	3.22	6.11
W.P.	5.00	2.28	5.33
W.M.	4.55	2.00	5.67
$\bar{x}$	4.85	2.47	5.40
SD	0.19	0.49	0.42
SE	0.08	0.20	0.17
Diff. from Control P =		0.001	0.05

TABLE IX

INSULIN AND HYDROCORTISONE INFUSION

	MINIMUM GLUCOSE MASS m mol/Kg		
Subject	Control	Insulin	Hydrocortisone
A.C.	0.922	0.935	0.978
W.W.	1.121	0.521	1.372
D.T.	1.049	0.807	1.586
C.L.	1.065	0.746	1.316
W.P.	1.255	0.907	1.187
W.M.	1.030	0.798	1.506
$\bar{x}$	1.074	0.785	1.324
SD	0.110	0.147	0.220
SE	0.045	0.060	0.090
Diff. from Control P =		0.02	0.05

TABLE X

INSULIN AND HYDROCORTISONE INFUSION

GLUCOSE REPLACEMENT RATE m mol/Kg/min

Subject	Control	Insulin	Hydrocortisone
A.C.	0.01505	0.01705	0.01239
W.W.	0.01294	0.01644	0.01711
D.T.	0.01139	0.01061	0.01722
C.L.	0.01194	0.01417	0.01250
W.P.	0.01267	0.02278	0.01278
W.M.	0.01261	0.02289	0.01650
$\bar{x}$	0.01278	0.01728	0.01472
SD	0.00122	0.00483	0.00239
SE	0.00051	0.00189	0.00100
Diff. from Control P =		0.06	insig

TABLE XI

INSULIN AND HYDROCORTISONE INFUSION

	GLUCOSE SPACE ml/Kg		
Subject	Control	Insulin	Hydrocortisone
A.C.	193.0	480.8	195.7
W.W.	231.9	191.6	259.9
D.T.	205.3	302.5	313.7
C.L.	220.3	231.5	215.4
W.P.	251.1	398.0	222.5
W.M.	226.1	398.9	265.8
$\bar{x}$	221.3	333.9	245.5
SD	20.4	111.0	42.9
SE	8.3	45.3	17.5
Diff. from Control P =		0.06	insig

TABLE XII

INSULIN AND HYDROCORTISONE INFUSION

HORMONE LEVELS

	Insulin μU/ml	Glucagon pg/ml	H.G.H. μg/ml	Cortisol μg/100 ml
Control	9.83 ± 4.62	58 ± 23	1.35 ± 0.79	9.15 ± 3.64
Insulin Infusion	76.50 ± 21.87	204 ± 57	21.32 ± 8.33	14.15 ± 5.21
Hydrocortisone Infusion	9.00 ± 3.69	51 ± 19	5.30 ± 3.56	46.78 ±13.41

TABLE XIII

Patient Data

Subject.	Age.	Height(ins).	Weight(Kg).	Surface Area(M^2).
AC	37	72	74.2	1.94
WW	28	76	79.6	2.10
DT	25	73	83.5	2.08
WP	38	74	76.0	2.00
WM	34	72	70.0	1.91
$\bar{X}$	32	73	76.7	2.01
SD	5.7	1.7	5.15	0.08
SE	2.5	0.75	2.30	0.04

TABLE XIV

Serum Glucose Concentration. m mol/l

Subject.	Control	A-Acid.	5% Glucose	25% Glucose.
AC	4.78	4.55	5.38	5.50
WW	4.83	4.55	5.89	5.94
DT	5.11	4.22	5.44	6.39
WP	5.00	4.83	7.00	8.33
WM	4.55	4.55	5.77	7.67
$\bar{X}$	4.85	4.54	5.90	6.77
SD	0.21	0.22	0.65	1.19
SE	0.09	0.10	0.29	0.53
Significant Difference from Control. P =		IS	< 0.03	<0.04

TABLE XV

Minimum Glucose Mass m mol/Kg

Subject.	Control.	A-Acid.	5% Glucose. 150g/day	25% Glucose. 750g/day
AC	0.922	1.240	1.322	1.584
WW	1.121	1.684	1.291	2.312
DT	1.049	1.090	1.133	2.462
WP	1.255	1.179	1.909	2.589
WM	1.030	1.077	1.710	3.375
$\bar{X}$	1.076	1.265	1.473	2.464
SD	0.123	0.250	0.323	0.641
SE	0.055	0.112	0.144	0.287
Significant Difference from Control. P =		IS	< 0.03	< 0.007

TABLE XVI

Glucose Replacement Rate m mol/Kg/min

Subject.	Control.	A-Acid.	5% Glucose. 150g/day	25% Glucose. 750g/day
AC	0.01505	0.01255	0.01455	0.02472
WW	0.01294	0.01050	0.01133	0.04600
DT	0.01139	0.01167	0.01061	0.04417
WP	0.01267	0.00844	0.01511	0.03061
WM	0.01261	0.01267	0.01383	0.06472
$\bar{X}$	0.01294	0.01117	0.01311	0.04205
SD	0.00128	0.00172	0.00200	0.04205
SE	0.00061	0.00078	0.00089	0.00694
Significant Difference from Control. P =		IS	IS	< 0.016

TABLE XVII

GLUCOSE SPACE ml/Kg.

Subject.	Control.	Amino-acid.	Glucose 150g/day.	Glucose 750g/day.
AC	193.0	272.2	245.4	270.1
WW	231.9	369.6	219.2	388.9
DT	205.3	258.1	208.2	385.3
WP	251.1	244.0	272.7	310.7
WM	226.1	236.3	296.0	440.3
$\bar{X}$	221.5	276.0	250.1	359.1
SD	22.80	54.07	36.56	67.88
SE	10.19	24.18	16.35	30.56
Significant Difference from Control. P =		Insig.	Insig.	0.01

TABLE XVIII

Mean Hormone Levels during Infusion

Group.	Insulin mg/ml,	H.G.H. mg/ml,	Glucagon pg/ml,	Cortisol µg/100ml.
Control.	9.8 ± 5.2,	1.12 ± 0.61,	65 ± 20,	7.9 ± 2.3.
A-Acid.	6.2 ± 2.4,	2.58 ± 3.14,	163 ± 98,	9.4 ± 3.6.
5% Glucose.	13.6 ± 7.9,	2.60 ± 2.29,	43 ± 36	7.0 ± 1.0.
25% Glucose.	37.2 ± 20.8,	1.86 ± 1.13,	23 ± 15	9.7 ± 2.5.

TABLE XIX

DATA ON CARBON-14 GLUCOSE FROM LITERATURE

Author	Date	Journal	Subject	Body Wt/Kg	m mol/kg Exchangeable Glucose Mass	m mol/kg/min Glucose Replacement Rate	ml/kg Distribution Volume
Shreeve	1956	Metabolism	N_1	72.0	1.055	0.00805	220.0
			N_2	65.0	1.500	0.00778	310.0
			N_3	90.0	0.944	0.00905	190.0
			N_4	65.0	1.167	0.00667	230.0
Reichard	1963	J.Biol.Chem.	N_1	47.7	2.611	0.02083	470.0
			N_2	50.5	1.889	0.01294	340.0
			N_3	85.5	1.389	0.01016	270.0
			N_4	73.6	1.833	0.01544	340.0
Searle	1969	Metabolism	C.F.			0.00872	
			K.N.			0.01055	
			J.H.			0.00905	
			V.P.			0.00750	
Long	1971	J.App.Physiol.	S.B.	61.2	1.289	0.01616	241.0
			G.R.	46.0	1.598	0.01289	130.0
			R.D.	55.2	1.760	0.01689	270.0
			W.B.	72.9	1.394	0.00539	242.0
			H.H.	108.2	0.708	0.00439	164.0
			L.M.	56.7	1.675	0.00917	171.0
			P.R.	66.0	1.540	0.01244	276.0
			V.M.	86.2	1.655	0.01394	206.0
			W.N.	66.8	1.347	0.01328	188.0
			A.P.	76.5	0.853	0.00561	177.0
			H.C.	55.9	1.312	0.01328	180.0
$\bar{x}$					1.448	0.01094	242.8
SD					0.432	0.00417	80.9
SE					0.099	0.00083	18.5
n					19	23	19

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RESEARCH HORIZONS IN HOSPITAL NUTRITIONAL SUPPORT

Protein Energetics, The Cellular Steal, and Cost-Benefit Analysis

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Additional applications and improved efficiency in parenteral feeding of hospitalized patients will depend on the capability of bioscientists in this field, and their ability to provide data for some of the outstanding questions that remain. In this brief abstract will be presented some of those questions.

There are two sets of questions. One set lies in the familiar biosciences area of nutrition and metabolism. The second set of questions lies in the social and economic sphere and has to do with an evaluation of the costs, risks, benefits and efficiency levels of this relatively new nutritional modality now being very widely applied.

Energetics of Protein Synthesis

Precisely what are the energy transactions involved in protein synthesis? How are these needs ideally met? Only about one-fifth of the energy involved in synthesis of peptide bonds (about 25 kcal/m) is released upon hydrolysis. The energy support structure for this transaction depends upon the regeneration of ATP and GTP from the oxidation of carbohydrate at the mitochondrial level. Why is it that a particular 6-carbon compound, glucose, appears to support this synthesis more efficiently than energy derived from other sources? Why does endogenous fat oxidation fail to provide adequate energy support for synthesis of peptide bonds as would be indicated by zero nitrogen balance? What is the relationship of protein synthesis energetics to endocrine governance of body fuel metabolism? Data gathered in this area of research is going to make it possible to design the parenteral feeding program for patients more accurately than at the present

time, possibly sparing some expense in the administration of amino acids not properly covered by exogenous energy sources for protein synthesis, and with efforts devoted to improving the endocrine "set" of the organism. Better to give less nitrogen and provide adequate energy cover, than to squander wasted amino acids?

Endocrinology of Acute Injury

Evidence suggests that the catecholamine discharge in response to acute tissue injury and blood volume challenge brings in its wake glucagon activation, insulin inactivation and cortisol stimulation that together produce macronutrient changes, in a sense, as a by-product. Circulatory failure (low flow states, traumatic shock, cardiac decompensation) is the primary stimulus of catecholamine discharge. Is it possible that some of these circulatory maladjustments provide the basic driving force for the post-injury metabolism? Can one continue to support the concept that gluconeogenesis from protein sources is the principal endocrine impulse for the alterations that follow trauma?

Draining an abscess may turn out to be the equivalent of three weeks of parenteral nutrition, but far more economical. Abating the stress, permitting normal anabolism, may be far more important than force feeding by vein.

Aggressive surgical and medical care, normalizing the physiologic maladjustment of the patient (i.e. restoration of blood volume, management of sepsis, immobilization of fractures, exteriorization of damaged hollow viscera, etc.) by abating the catecholamine component of injury may be the most important metabolic and nutritional step that the surgeon and physician can take.

Relationship of these endocrine changes to the synthesis of muscle and visceral protein on the one hand, and soluble protein such as the coagulation cascade and immunoglobulins, must be worked out. It has been assumed that synthesis of new protein in muscle is sometimes done at the expense of "acute phase" proteins elsewhere in the extracellular phase. Evidence for this concept is wanting.

Anabolic "Set" Versus Net Anabolism

Evidence needs to be gathered on the concept of "high priority" proteins, and the possibility that they may be actively synthesized while other proteins in the body are still undergoing net degradation. In such a situation a favorable anabolic "set" for acute phase proteins could be said to exist in the face of net nitrogen loss. Several evidences at the present time favor this possibility; but hard evidence is lacking. There have been spotty reports that even tiny amounts of glucose somehow have an adverse effect on albumin synthesis, even when added to huge (i.e. isocaloric) amounts of amino acids. Against this evidence is the finding that modest amounts of glucose favor whole body protein synthesis, either expressed in absolute terms or as a fraction of net turnover.

In any consideration of trauma as a stimulus to metabolic change, it is important to differentiate sharply between modest degrees of operative injury (closed elective, uneventful, clean civilian surgery) on the one hand, and very severe tissue injury (multiple fractures, stabs, bullet wounds, military injuries and burns) on the other. The latter group of major traumata impose an altered mandate for body fuel utilization, whereas the smaller degrees of injury do not.

Methods for study of these aspects in nutrition are still very unsatisfactory. Isotopic equilibrium methods by prolonged infusion seem preferable to the single pulse injection; local tissue biopsy in the study of isotopic incorporation in the specific protein molecules may prove to be an improvement. The latter may become more readily available as the gas chromatograph-mass spectrometer (CGMS) becomes more widely available. The study of body composition by isotope dilution is not a good method for studying short changes in nutrition, because of the intrinsic random errors of the method. For short term changes, metabolic balance techniques with added isotopic infusion seem preferable but suitable allowance must be made for the intrinsic assumptions and errors of these methods also.

Cellular Steal Syndrome

With nutritional support the intracellular synthesis of protein and other cytoplasmic components begins, often at a brisk rate. If certain trace elements and vitamins are not available in the extracellular fluid in adequate amounts, the ECF and plasma levels of these substances may be acutely reduced during anabolism. The cells are, in a sense, robbing the extracellular fluid of the needed ingredients, because they are not being provided externally. This is the "cellular steal syndrome" and is most clearly seen in the case of zinc. The person with global severe starvation (protein calorie malnutrition) may show few signs of zinc deficiency. When anabolism begins on parenteral nutrition, a severe zinc deficiency with all the skin changes and a lowering of the plasma zinc concentration may ensue. While zinc deficiency is a result both of alterations in total body zinc and plasma concentration, the peripheral clinical signs are accentuated when the plasma zinc falls. This may happen at the very time that the patient looks better in every other way and is beginning to anabolize protein. The cells have stolen zinc from the extracellular fluid. The "cellular steal syndrome" also applies to magnesium, potassium and possibly trace minerals such as manganese, cobalt, chromium and copper. It may also apply to some of the vitamins that act as cofactors in enzyme reactions, particularly folate. "Balanced unstressed protein calorie malnutrition" rarely shows up with monovalent or single-substance deficiencies. When, however, an overall cellular synthesis is begun by providing macronutrients but without some one essential cofactor, then the monovalent deficiency can become immediate and severe.

Immunologic Overtones of Macronutrient Change

Severe degrees of global starvation, even to the point of imminent fatality, can be associated with maintenance intact of certain immunologic parameters as shown by study of concentration camp inmates at the end of World War II. On the other hand, even transient episodes or antigenic overloads can be associated with loss of all delayed hypersensitivity reactions. Finally, certain trace minerals such as zinc, if deficient, may be associated with a reduction in delayed cutaneous hypersensitivity.

One must regard with suspicion the concept that all nutritional deficiencies are accompanied by immunologic disorders or restoration of these immunologic disorders indicate that nutrition has been restored.

A number of studies have indicated that patients who enter a surgical or medical experience without normal delayed skin hypersensitivity are at higher risk. Is this cause and effect or merely an association of two disorders? Wherever immunologic crippling can be corrected by nutritional means, this should be done. But it is important not to overlook the other infectious and hematopoietic aspects of such immunologic deficiency.

Social and Interactive-Aggressive Aspects of Nutritional Care

The field of nutrition is so concerned with avoidance of "malnutrition" that fads and fancies become readily established. This is probably more true in nutrition than in any other field of patient support such as transfusion, infusion, coagulation, endocrine substitution, etc. This is particularly true because "malnutrition" often eludes definition. An athlete entering training at the beginning of the season will lose muscle mass, body cell mass and body fat and be in superb physical condition. A patient losing exactly the same fraction of body weight due to cancer of the stomach will be "malnourished."

As a result of this tendency towards enthusiasm amongst nutritionists, dietitians and physicians, there is a tendency toward overloading of the circulation, the use of nutrition instead of aggressive surgery (undue surgical procrastination based on a central venous catheter), and lack of adequate attention to cost benefit relationships. The use of such terms as "kwashiorkor" or "marasmus" to characterize everyday hospital patients is a form of subtle coercion towards more aggressive nutritional management. When such terms, originally used to denote specific advanced forms of starvation, are employed to describe hospital patients with far more complex illness/injury interactions, often less severe on the nutritional side, there is a danger of oversimplification.

The enthusiastic and aggressive nutritionist may become blind to the undrained subphrenic abscess.

Research needs to be done in this area of nutrition, analyzing the interplay between enthusiastic investigators, aggressive dietitians, and pharmaceutical firms anxious to sell their products. It is not enough publicly to question how much effort should be expended to save the body a few grams of nitrogen. Rather, the question should be asked as to how often workers in this field become so imbued with nutritional zeal as to overlook other aspects of the medical and surgical care of their patients.

In addition, some sort of carefully planned alternate-case research should be carried out to determine the benefits of hospital intravenous nutrition in marginal cases. Some attempts have been made along this line, usually addressed to morbidity or mortality statistics, or day of discharge. It seems unlikely that such gross measures will ever provide a satisfactory answer to these social and economic questions.

If one considers all the patients in the hospital as occupying a spectrum of risk, cost and benefit in parenteral nutrition, then the nature of the descriptive research becomes clearer. There is a large central group in whom needs are difficult to define and benefits hard to measure. This is where the research should be focused. By contrast, there are two opposite ends to this curve: patients in whom parenteral nutrition is clearly life-saving or life-maintaining, and has proven to be the turning point in their management; and, contrariwise, at the other end of the spectrum, a group of patients who could perfectly well tolerate the transient caloric deficiency and loss of body nitrogen that would result from the avoidance of intravenous feeding. Patients with cancer may be a special group. Support during chemotherapy may be justified for specific gastrointestinal effects, wholly aside from any malnutrition that may be involved.

Short term changes in albumin, immunoglobulins, skin hypersensitivity and urinary nitrogen excretion may be misleading because of short term fluctuations in all of these, and the fact that they are influenced by other factors, especially dilution.

Work in this field should be developed toward use of this important weapon of parenteral nutrition, in a way that is most effective in terms of patient benefit. This research will be difficult to carry out, and will arouse criticism and controversy. If research of this type is not begun by those working in nutrition, it is apt to become a part of the current governmental pressure for blind budgetary and cost control, and react in a way that is undiscriminating and unfavorable to patient welfare.

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APPENDIX B

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